Hospital Library

ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 13 (O.S., Vol. XVIII) NOVEMBER, 1939 NUMBER 5

CONTENTS

	Page
Vitamins in Theory and Practice. Howard B. Lewis	749
A Discussion of a Therapeutic Test and a Provocative Test in Gouty Arthritis. L. Maxwell Lockie	755
A Statistical Study of Allergy in Arthritis. Eugene F. Traut and Emil G. Vrtiak	761
Active Immunization against Tetanus. Herman Gold	768
The Effect of Roentgen-Ray on the Blood Codehydrogenases I and II. William B. Bean, Richard W. Vilter and Tom D. Spies	783
The Use of Dilantin in the Treatment of Epilepsy. O. P. Kimball and T. N. Horan	787
Some Studies in the Mechanism of Cardiac Hypertrophy. George Herrmann and George M. Decherd, Jr.	794
A Method of Testing Cardiac Function. Dan G. Stine	807
Roentgen Procedures Useful in Cardiac Diagnosis. Fred Jenner Hodges	826
Deep Injection of Novocaine for the Relief of Pleural Plain. Sidney Schnur	845
Initial Management of Tuberculosis with Special Reference to the Psychology of the Patient. Lewis J. Moorman	849
The Limitations of Government in Medicine: The San Francisco Experience. J. C. Geiger, A. E. Larsen and J. P. Gray	856
Case Reports:	
Congenital Hemolytic Jaundice; Report of a Case of Congenital Hemolytic Jaundice; Initial Hemolytic Crisis Occurring at the Age of 75; Splenectomy Followed by Recovery. Harry Mandelbaum	872
Histologically Non-Malignant Metastasizing Hemangioma, with Report of a Case. Maurice James Abrams	883
Infectious Mononucleosis Complicating Typhoid Fever. Alfred S. Schwartz and Bernard Lidman	895
Editorial	899
Reviews	902
College News Notes	904

Subscription per volume or per annum, net postpaid, $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico; $7.50, other countries.

Entered as Second Class Matter at the Post Office at Lancaster, Pa. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1926.

GALACTOSE

This carbohydrate has found widespread clinical use as an indicator of the degree of liver function in the "galactose liver function test." More recently it has also been demonstrated that laboratory animals fed a diet high in galactose develop a type of nutritional cataract.[1-4] The ability to produce cataract by nutritional means will no doubt play an important rôle in further research on the etiology of cataract in the human.

General Biochemicals' galactose is available in bulk quantities for clinical or laboratory research at special low prices.

Upon request, we shall be pleased to send our list of biochemicals of nutritional interest.

1. Mitchell, H. S., *J. Nutrition*, 9:14 (1935).
2. Yudkin, A. M., and Arnold, C. H., *Proc. Soc. Exp. Biol. Med.*, 32:836 (1935).
3. Bellows, J. G., and Rosner, L., *Am. J. Ophth.*, 20:1109 (1937).
4. Mitchell, H. S., and Cook, G. M., *Arch. Ophth.*, 19:22 (1938).

GENERAL BIOCHEMICALS, INC.

418-M REPUBLIC BUILDING, CLEVELAND, OHIO

ANNALS OF
INTERNAL MEDICINE

VOLUME 13 NOVEMBER, 1939 NUMBER 5

VITAMINS IN THEORY AND PRACTICE*

By HOWARD B. LEWIS, PH.D., *Ann Arbor, Michigan*

OUR conception of the vitamins has undergone material change since the term was introduced into the literature of the biological sciences and medicine by Casimir Funk in 1912. In an important review of the existing knowledge of beri-beri, scurvy, and pellagra, he emphasized the reality of the deficiency diseases and suggested the term "vitamine" for the factors, as yet poorly characterized, which were effective in the cure or prevention of these conditions. The term was intended to suggest their vital function (*vita*, life) and basic nature (amine, a basic compound containing nitrogen). Since early investigations failed to support Funk's contention of the basic nature of vitamines in general, the final "e" was dropped by common consent, and to avoid what appeared to be an unjustifiable connotation, the spelling vitamin was adopted. It is perhaps not without interest to note that 15 years elapsed before the presence of nitrogen in any vitamin was demonstrated. Several of the vitamin factors are now recognized as compounds of nitrogen and the correctness of Funk's term for certain vitamins is thus established.

The term vitamin entered the medical literature as a negative factor, i.e., the vitamins were considered to be substances, preventive or curative, of certain diseases of unknown etiology and hence were designated as antineuritic, antiscorbutic and the like. Particularly striking was the fact that the effects obtained by the use of these new dietary factors were far more marked than those shown by corresponding amounts of the more common nutrients (fats, carbohydrates, proteins and salts) and quite out of proportion to the amounts evidently present in the food. The importance of the "little things in nutrition" (Mendel) was thus realized. With the development of the modern science of nutrition came the recognition that these factors, originally defined in relation to pathology, were essential for the maintenance of the normal state of well-being of the organism. Our point of

* Read at the New Orleans meeting of the American College of Physicians March 27, 1939.

From the Department of Biological Chemistry, Medical School, University of Michigan.

Copyright, 1939, by The American College of Physicians

view in the study of vitamins thus changed from the negative aspect (they were no longer "anti—s"), to the positive (they were requisite factors for normal nutrition).

With the clearer recognition of the chemical nature and properties of the vitamins, the term "chemical regulators" as applied to this group has become significant. The characterization of the hormones as "chemical messengers" (Bayliss and Starling) or chemical regulators, definite chemical factors for the integration of the reactions of the various organs and tissues, has long been accepted. It seems probable that, in the near future, vitamins may be best characterized as chemical regulators of *exogenous* origin, in contrast to the hormones, chemical regulators of *endogenous* origin. Thus the higher forms have the power to synthesize the hormones, thyroxine, insulin or the various sex sterones, with relative ease from precursors, at present not definitely known but presumably of lesser complexity. The vitamins or exogenous chemical regulators, on the other hand, must be made available to the higher organisms as such or in the form of closely related precursors, i.e., the provitamins. The fact that a supply of preformed vitamins or precursors in the diet is not essential for some species is recognized, but its explanation is not clear. Thus the white rat does not require ascorbic acid (vitamin C) in the diet and since the tissues of these animals contain the vitamin, its synthesis by this species must be assumed.

The original vitamin nomenclature was an alphabetical one, the order being with few exceptions primarily that of the discovery or recognition as an individual factor. This alphabetical nomenclature was further modified by qualifying adjectives indicating simple properties, fat- or water-soluble, heat-labile or heat-stable, and by adjectives suggesting the pathological condition occasioned by the absence of the vitamin from the diet. As our knowledge of the chemistry of the vitamins was extended by isolation, identification and synthesis, the older indefinite names have been replaced by more specific ones. Thus the water-soluble anti-scorbutic vitamin C has been designated as ascorbic acid by Szent-Gyorgyi, who was one of the first to isolate it in pure form. Similarly the heat-stable growth-promoting fraction of the B complex, B_2 or G, is now known as riboflavin.

A primary requirement for progress in the study of vitamins has been the successful experimental production of the deficiency disease in laboratory animals. With such a procedure available, it has been possible to study the occurrence and distribution of vitamins in natural foodstuffs by the use of biological assays based upon effectiveness in the prevention or cure of the associated deficiency disease. Foods were thus characterized as rich, good or poor sources of vitamins. Such classifications were, of necessity, crude since the importance of standardization of experimental procedure was not realized. Ultimately uniform methods of assay were adopted and units of vitamin content which permitted more exact comparison of results from different laboratories were agreed upon. The basis of these units was, however, a biological one; the unit was defined in terms of animal behavior

(growth response, curative or preventive effect) and no absolute evaluation of the various units was possible.

It was evident that if the vitamin theory was to be placed upon a scientific basis, more exact chemical knowledge of their nature and properties was necessary. The studies of the distribution of vitamins in nature had shown in many instances foodstuffs unusually rich in their vitamin content and thus suggested materials from which success in the isolation of the vitamin might be anticipated. Valuable information as to probable chemical properties was provided by investigations of the stability of the vitamins, particularly towards heat and oxidation.

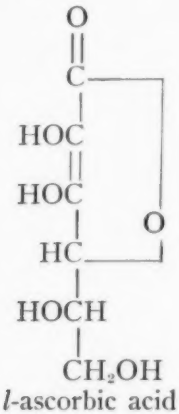
The isolation of the pure vitamin, the determination of the chemical structure and the laboratory synthesis of the vitamins have now been achieved in several instances. The progress in this field since the isolation and chemical characterization of vitamin C (ascorbic acid) in 1933 is notable.

With the knowledge of the chemical nature of the vitamin, chemical assays of the vitamins have in many cases replaced the slow and difficult methods of biological assay. No longer is the vitamin unit defined exclusively in terms of animal behavior but in absolute terms of the content of a specific chemical substance. With such methods available, it has been possible to assay materials which did not readily lend themselves to the methods of biological assay. The vitamin content of blood and tissues, the storage and excretion under physiological and pathological conditions, and the relation of the supply of vitamins in the diet to the maintenance of the vitamin balance may now be determined rapidly and conveniently. If the methods of chemical analysis prove to be as specific as is expected, detailed knowledge of the vitamin economy of the organism should be possible, knowledge as exact as that now obtainable for such simple chemical elements as chlorine or calcium. However, until such a specificity of the methods of chemical assay is conclusively demonstrated, recourse must still be had to the specific animal tests in order to check the chemical tests and to avoid any misinterpretation of the latter.

With the clarification of the problem of the chemistry of the vitamins, the investigations now turn again to the biological aspects. What are the functions of the vitamins? If they are to be regarded as exogenous chemical regulators, what is the basis, chemical and physiological, for the function of each? How are these functions altered in disease? How are the vitamins related to the endogenous chemical regulators, the hormones? Why does a group of atoms, combined in a definite molecular structure, manifest a highly specific physiological activity? To what extent will modification of this chemical structure alter the physiological activity? Will it be possible by the methods of synthetic organic chemistry to obtain compounds superior in activity to the naturally occurring substances? These are unsolved problems, common to both vitamin and hormone studies. They represent one phase of the general problem, the relation of chemical constitution to physiological action. The solution will not be simple, but we may anticipate marked progress.

It is not possible to discuss in detail each individual vitamin factor in relation to the development of the vitamin hypothesis. This has been done elsewhere, particularly in the recent series of articles by well-known workers in the *Journal of the American Medical Association.* It is desired to trace at this time the evolution of our knowledge of one of the vitamins, vitamin C, in the light of the general considerations just presented.

Scurvy had for many centuries been recognized as a disease due to improper diet and correctly so. It was well known, especially among sailors, that outbreaks of scurvy were frequent after deprivation of fresh foods for long periods of time and that prevention was possible and rapid cure effected when ample supplies of fresh vegetables and fruits were available. Notwithstanding this recognition of the relation of scurvy to diet, the nature and properties of the antiscorbutic substances in fresh food were unknown. In 1907, Holst and Frölich showed that scurvy could be produced at will in young guinea pigs by feeding a diet consisting of grains exclusively, and that experimental scurvy, thus produced, could be promptly cured by supplements of fresh vegetables or fruit juices, notably cabbage and the juices of the citrus fruits. A means of study of the occurrence and distribution of the antiscorbutic dietary principle was thus at hand. It was soon recognized that the vitamin, designated in the alphabetical nomenclature as water-soluble C, was not stable, being easily destroyed by heat, and that this destruction was greatly accelerated in an alkaline reaction and in the presence of oxygen or air. This suggested that the vitamin was a strongly reducing substance readily oxidized, particularly in the presence of alkali. In investigations at the Lister Institute in London, it was noted that in the concentration of lemon juice, the increases in the reducing power were parallel to the increases in the antiscorbutic potency. This was followed by the isolation in crystalline form of the vitamin from lemon juice, adrenals and paprika. The challenge offered by the isolation of this, the first vitamin to be obtained in crystalline form, was accepted by the organic chemists of Europe and in less than a year, the structure of the vitamin, named by Szent-Gyorgyi *ascorbic acid,* was known and its synthesis in the laboratory successfully achieved.



l-ascorbic acid

As had been predicted from the behavior of the vitamin in plant juices, ascorbic acid was a strong reducing agent and, by oxidizing agents, was converted to an oxidation product with a loss of antiscorbutic properties.

It was now possible to seek for a chemical method of assay to replace or supplement the biological assay (production or cure of scurvy in young guinea pigs). Tillmans had made use of the reduction of a dyestuff in order to determine the freshness of fruit juices. It is now known that ascorbic acid reduces readily certain reversible dyes of high oxidation potential (notably *p*-dichlorophenolindophenol). It is thus possible to determine the vitamin C content of a plant or animal tissue by titration with the dye. While the method is not absolutely specific, parallel assays by the chemical and biological methods have demonstrated the value of the chemical procedure.

By the use of this chemical method, the ascorbic acid content of urine, blood and animal tissues, materials which are unsuited for biological assay, may be determined. It has also been shown that this procedure may be applied to histochemical studies. The methods of histochemistry, developed in the Carlsberg laboratories in Denmark, whereby analysis of microtome sections of tissue are possible, have been employed with certain animal tissues (adrenals, pituitary) by Glick. The concentrations of ascorbic acid in the various regions of the glands, the relative numbers of cells in the sections and the vitamin content per cell have been estimated. The contrast between the data of 1929, in which the vitamin C content of the foodstuffs was characterized by such approximations as 0 to ++++, and those of 1939, in which the content of ascorbic acid *per cell* in various zones of organs is stated in chemical terms, is convincing evidence of the progress in vitamin study and of the validity of the vitamin theory. It must be remembered that not until 1919 was the concept of scurvy as a specific vitamin deficiency disease generally accepted. The existence of subacute vitamin deficiency is now generally recognized and the importance of tests which would permit prompt recognition of these states of sub-optimal nutrition is obvious. Studies of urinary excretion of vitamin C have indicated marked individual variations and have suggested that the degree of saturation of the tissues with ascorbic acid is an important factor in determining urinary excretion. The ascorbic acid content of the blood and urine may be abnormally low when the intake of ascorbic acid is significantly less than the normal requirements. As the intake of ascorbic acid is increased and as the state of tissue saturation is approached, the urinary excretion shows progressive increase until, at saturation, an abrupt rise in the ascorbic acid of the urine is noted. The amount of dietary ascorbic acid necessary to induce saturation appears to be an index of the vitamin C nutrition of the individual. While all workers are not in entire agreement as to the details of such a test, it appears to be of real value in the study of subacute scurvy.

What is the function of ascorbic acid in the animal organism? It appears to be most concentrated in actively functioning tissues, the cortex of

the adrenals, hypophysis, thyroid, corpus luteum and other glands. Its strong reducing action suggests a relation to oxidative processes, to cell respiration. With the chemical background well established, advances in our knowledge of the function of ascorbic acid and of its relation to other vitamins and hormones may be anticipated.

The story of the development of our knowledge of the other vitamins is similar to that outlined for ascorbic acid. New concepts are being introduced. A multiplicity of vitamin factors is suggested. Until investigation has shown the presence of a specific chemical agent of known structure, the existence of a vitamin factor must be questioned. Three components of the water-soluble vitamin B, now referred to as the B complex, have been isolated in crystalline form and the existence of several others has been suggested. B_1, the antineuritic vitamin (thiamin or aneurine), B_2, the growth-promoting factor (G or riboflavin) and nicotinic acid, important in the treatment of human pellagra, are all well characterized.* Each seems to be an essential component in an important enzyme system in nature. It is of interest that the inability to reproduce experimentally in animals the pathology of human pellagra delayed progress in the recognition and treatment of pellagra as a deficiency disease. Chemical methods for the determination of thiamin and nicotinic acid have been presented and valuable information concerning the saturation of the tissues and the urinary excretion of these vitamins will shortly be at our disposal.

The nutritional and chemical backgrounds for continued vitamin investigations are available. The vitamins, natural or synthetic, are readily obtainable. It is for the clinician to make use of the information supplied by the investigations of experimental biology, both for the maintenance of normal nutrition and for the treatment of the deficiency diseases, acute and subacute. The place of vitamins in *normal nutrition* is concerned with their rôle as components of the natural foodstuffs. Careful selection of the diet should make possible an abundant supply of these important essentials. The rôle of vitamins in conditions of *acute deficiency* is that of drugs, by means of which the vitamin balance of the organism shall be restored to normal as rapidly as is possible.

There is, however, a grave danger that in our enthusiasm over the achievements, experimental and clinical, in the vitamin field, we forget that the vitamins comprise only one group of the many substances essential for the normal nutrition and that all the vitamins of the alphabet cannot make good a deficiency in the other important dietary constituents, minerals, protein, fats and carbohydrates. We would do well to bear in mind the warning of Professor Sherman of Columbia University with reference to excessive zeal in the use of vitamin D: "Confidence in the value of the anti-rachitic vitamin must not lead to any lack of care in providing a liberal supply of calcium and phosphorus during growth."

* Since this paper was presented, the isolation and synthesis of crystalline vitamin B_6 has been successfully achieved. This compound, like nicotinic acid, is a pyridine derivative.

A DISCUSSION OF A THERAPEUTIC TEST AND A PROVOCATIVE TEST IN GOUTY ARTHRITIS *

By L. Maxwell Lockie, M.D., F.A.C.P., *Buffalo, New York*

The first part of this paper will be devoted to a discussion of the effect of colchicine on gouty arthritis. The second part concerns the use of a diet high in fat, low in carbohydrate, and low in protein as a means of provoking attacks of gouty arthritis in some gouty patients.

During the past 10 years the physicians of the United States have realized the apparent increase in the number of cases of gout and the occurrence of a symptom of gout—namely gouty arthritis. Before the work of Hench,[1] it was thought by many to be a disease which existed only in Europe, especially in England. Now, woe betide the physician who does not consider gout very seriously in every male patient who complains of arthritis. It is estimated that 96 to 98 per cent of gouty arthritis occurs in males. The most important single aid in the diagnosis is the history of recurrent arthritis with complete relief from symptoms between attacks. Particular emphasis must be placed on the words "complete relief." The joint symptoms of rheumatic fever also vanish completely but that disease usually occurs before the age of 25 years whereas gouty arthritis most frequently occurs after 25 years of age. Tophi containing sodium urate crystals are found only in gout. The blood uric acid may be increased above 5 mg. per cent in the early cases and is usually increased in the later cases. Roentgen-ray findings, provocative and therapeutic tests may be helpful.

There are a few drugs used in medicine which act specifically in the treatment of disease, for example, quinine in malaria. Colchicine is a drug which quickly relieves the acute symptoms of gouty arthritis. It has been used for thousands of years—mention of it is made in the Ebers Papyrus 1550 B.C. During the past 75 years the wine of colchicum, which contains colchicine as the active ingredient, has been preferred, but more recently the tablets of the alkaloid colchicine are widely used. A more accurate dosage is available in the tablet form. The mode of action of colchicine is not known.

In the experiments the drug was given in divided doses over a period of 24 to 72 hours until the patient had diarrhea. This was considered to be a sign that a full dose had been administered. Diarrhea often occurred after very few doses of one milligram (gr. 1/60), whereas others could take the drug for several days before the catharsis occurred. The drug was discontinued after the onset of the diarrhea.

* Read at the New Orleans meeting of the American College of Physicians March 30, 1939.

From the Buffalo General Hospital and the University of Buffalo Medical School.

One hundred and twenty-five cases were studied. One group consisted of 75 private patients with proved gouty arthritis and the other group was composed of 50 patients with other forms of arthritis taken from the Arthritis Clinic of the Out-Patient Department of the Buffalo General Hospital. Tophaceous and non-tophaceous gout were included. The diagnosis was made according to the criteria described by Hench.[1] All patients, except those few seen in the first attack, had a typical history of recurrent arthritis with complete relief from signs and symptoms between attacks. Tophi, when present, were examined for sodium urate crystals before they were considered to be diagnostic of gout. The blood uric acid usually was above 5 mg. per cent. The response to colchicine was uniform in the group of gouty patients. All experienced marked relief of the acute symptoms beginning about the time of the diarrhea. Instead of continually shifting in an effort to find a more comfortable position the patient could now move the involved joint with less pain. The sensitiveness of the skin around the joint was markedly decreased. Although the patient became much more comfortable not all of the symptoms were gone within 24 hours. During the next few days the stiffness and aching usually disappeared. Many of these patients had taken other forms of medication with little relief. Practically all had used acetylsalicylic acid or sodium salicylate with transient improvement only. Cinchophen was used by some and gave more relief than the acetylsalicylic acid. Three patients had marked urticaria and swelling following administration of the cinchophen. All noticed that the relief from colchicine was far more effective than from either the salicylate or cinchophen preparations.

The 50 patients from the Arthritis Clinic of the Buffalo General Hospital with various forms of arthritis other than gouty arthritis were given full doses of colchicine. They had been given acetylsalicylic acid or sodium salicylate medication previous to this study. The colchicine was given in a large enough quantity so that all the patients had diarrhea within 72 hours.

The cases of arthritis were divided as follows:

Atrophic (rheumatoid or chronic infectious)	21 cases
Hypertrophic (osteoarthritis)	14 cases
Menopausal	7 cases
Spinal (not hypertrophic)	5 cases
Gonorrheal	1 case
Fibrositis	2 cases

In no case of arthritis was there a dramatic relief of symptoms. A few had transient, mild relief during the active state of catharsis but the next day the pain returned with all of its former severity. No patient experienced enough relief to want to take the drug again. Those patients with the shoulder muscle pain of menopausal arthritis and fibrositis seemed to have comparatively more relief than others studied in this group.

A chart showing the effect on pain is given below.

Effect on Pain	No Relief	Slight Relief	Marked Relief
Gouty arthritis	0	0	75
Atrophic arthritis	17	4	0
Hypertrophic arthritis	14	0	0
Menopausal arthritis	3	4	0
Spinal arthritis	3	2	0
Gonorrheal	1	0	0
Fibrositis	0	2	0

In summary, colchicine acts in an unknown manner in the human body. It has a specific therapeutic effect in relieving the symptoms of gouty arthritis. There may be a mild transitory relief in some of the other forms of arthritis but it is never marked nor lasting.

The second part of this study is concerned with the precipitation of attacks of gouty arthritis by means of a special diet. In 1935 Lockie and Hubbard [2] reported studies on four patients with gouty arthritis to whom a high fat diet had been given. This work was suggested by the observations of Harding [3] who noted an increase of the blood uric acid in patients on a diet low in carbohydrate, low in protein and high in fat content. Lennox [4] noted the same effect in patients in a starvation state.

The experiments reported in 1935 will be briefly summarized as well as the results of five similar experiments carried out within the past six months.

Conditions of the experiments:

1. Positive diagnosis of gout with gouty arthritis.
2. No attack to be expected at the time.
3. No medication with the salicylate or cinchophen groups for two weeks previously.
4. Diet:

   Low in carbohydrate
   Low in protein (low in purine)
   High in fat

5. Codeine used only for relief of pain.

Experiment 1: E. H., a man, aged 52, had recurrent gouty arthritis of the feet, knees and hands since 1912. There was complete recovery between attacks. Tophi containing sodium urate crystals were removed from the left ear lobe. The blood uric acid was 6.0 mg. per cent (whole blood method).

The interval between attacks of gouty arthritis had been approximately a year. After a period of two weeks had elapsed following the present attack, he was given a diet of C 50, P 50, and F 220. On the seventh day there was marked pain, swelling and tenderness in the joints of the feet and ankles. The uric acid rose from 5.5 mg. per cent to 8.0 mg. per cent. Four days later the diet was changed to C 380, P 60 and F 130. Within two days marked improvement took place. The blood uric acid continued to remain elevated for 14 days, then gradually fell to the preëxperimental level. There was no further exacerbation of pain.

Experiment 2: W. R., a man, aged 28, had recurrent gouty arthritis for four years, usually following strenuous exercise, alcoholic debauch or thorough chilling. He

stated that during an attack there was marked swelling, pain and tenderness which would disappear within 10 to 14 days. The blood uric acid was 6.2 mg. per cent at the time of his last attack.

After recovery from this flare-up he stated, judging from past experience, that he would not have another attack for some months. Consequently we felt justified in administering the diet of C 60, P 60 and F 230 one week after recovery from this last attack. Within three days he felt poorly, the left hand, knee and small joints of the left hand became swollen and painful. It was necessary for him to go back to bed. No medication was given but the diet was changed to C 400, P 70 and F 60. There was marked improvement in 48 hours. He had no other attack of gouty arthritis during the next five months, at the end of which time he left the city.

Experiment 3: A. A., a man, aged 74, had recurrent gouty arthritis during the past 23 years. The blood uric acid was 6.8 mg. per cent. No tophi were present. Intervals between attacks were at least 10 months.

At the end of one week he was given a diet of C 20, P 30 and F 300. Within 48 hours the foot became swollen and tender. No medication was given but the diet was changed to C 350, P 60 and F 8 and within 72 hours all signs and symptoms had disappeared.

Experiment 4: After the above-mentioned patient had been free of pain for one week he agreed to resume the diet with the high fat content. Within 48 hours he had another attack and following a change to the diet containing the high carbohydrate proportion he became entirely well. There was little change in the blood uric acid during this experiment, possibly owing to the fact that he was on the high fat diet such a short time.

Experiment 5: N. G., a boy, aged 16 years, had tophi in both ears in 1932. Two years later he experienced his first attack of gouty arthritis. Three similar episodes occurred within three months. When he was seen three months following the initial attack he had many tophi containing sodium urate. The blood uric acid was 7.6 mg. per cent.

A week following recovery from the last attack he was given a diet of C 50, P 50 and F 250. At the end of 13 days he developed a very severe attack of gouty arthritis involving many joints. The blood uric acid increased from 8.6 mg. per cent to 16.0 mg. per cent. A diet high in carbohydrate did not alter the blood uric acid but within two days the patient felt better. It was necessary to give sodium salicylate before the blood uric acid returned to the former level.

Experiment 6: E. H., same patient as in experiment 1. During the past four years he was seen in the Out-Patient Department regularly. His diet was high carbohydrate, moderate protein (with low purine) and fairly low fat content. He took acid acetylsalicylic 0.30 gm. (gr. V) four days weekly, and used colchicine if he had any twinges of pain. During this period he had not experienced any severe attacks of arthritis. While convalescing from a cerebral accident he was given a diet of C 50, P 50 and F 250 for five days without provoking a flare-up in his joint symptoms. The patient left the hospital at this time; consequently the experiment could not be continued. However, this case should be included in view of the following experiments in which three attacks of gouty arthritis were produced within 48 hours of the beginning of the high fat diet in other gouty patients.

Experiment 7: J. C., a male, aged 54 years, has had recurrent arthritis with symptomless periods in between. Both big toe joints, ankles, knees, shoulders, elbows and fingers have been involved at various times. There was some limitation of motion of the right ankle due to tophi formation in the small bones. Tophi containing sodium urate crystals were present in the left ear lobe, left olecranon bursa, and on the dorsal surface of the left index finger. The blood uric acid was 5.0 mg. per cent. He had been free of any pain or discomfort from 1933 until November 15, 1938,

at which time he began to notice pain in the left hand and the left shoulder. A diagnosis of gouty arthritis was made.

On December 15, 1938 he was given a diet of C 35, P 50 and F 250. Within 48 hours he had severe pain in the right knee, right ankle and left hand, and during the next 24 hours the knee joint became filled with fluid. Two days after the high fat diet was started the temperature, which previously was normal, began to rise until it reached 103° F. on the fourth day of the diet. During this period the patient was so ill he could neither eat nor sleep. It was felt necessary to stop the high fat diet and give all the treatment possible to relieve the extremely severe attack. The pain subsided promptly upon administration of full doses of colchicine and a change to a high carbohydrate diet, but muscular stiffness persisted for a short time. The temperature became normal three days after institution of therapy. The level of blood uric acid did not vary.

Experiment 8: During the following month the above patient felt well. He was again placed on a diet of C 35, P 40 and F 250, and low in purine content. Sixteen days later he had a very severe attack of gouty arthritis involving many joints of the body—especially the right ankle, the left shoulder and the right knee which again filled with fluid during a 12 hour period. Even the area about the tophi in the left ear was very sensitive. The body temperature again began to rise, reaching a peak of 102° F. within three days; with change of diet to C 350, P 50 and F 70, and colchicine in full doses, his temperature gradually returned to normal within three days and his symptoms were relieved. There was little fluctuation of his blood uric acid during this time.

Experiment 9: N. G., the same patient as in experiment number 5. He had been quite comfortable during the following four years except for a steady progression of tophus formation. No severe attacks had occurred during the past year. He was admitted to the hospital for correction of deformity of the right knee joint as the result of tophus. During the first 24 hours the patient was given a high carbohydrate diet, then it was changed to C 43, P 30 and F 180. After 48 hours he began to be restless and felt poorly. The body temperature began to rise and he had extreme pain in many joints. Within three days the temperature had reached 102.4° F. and the pain had become more severe. The diet was changed to C 200, P 30 and F 35, and colchicine was given in large doses. The temperature dropped to normal within 48 hours and the patient was comfortable. There was a slight increase in the blood uric acid.

Experiment 10: The same patient was given a high fat diet after a period of 10 days during which time he had had no pain, nor was any medication used. Again within 48 hours his temperature began to rise and he had severe pain in many joints. This became progressively worse so that at the end of another 48 hours his temperature was 101.2° F. and many joints of his body were involved. He had pain around the tophi in the left ear. Again the diet was changed to one high in carbohydrate and low in fat content. Full doses of colchicine were given and within 48 hours his symptoms disappeared. During this time his temperature became normal. No further medication was necessary.

Conclusions

1. Colchicine in sufficient doses to cause diarrhea relieves the signs and symptoms of gouty arthritis in a dramatic manner.

2. The administration of a low carbohydrate, low protein, high fat diet to patients with gout provoked an acute attack of gouty arthritis in nine of the 10 experiments.

REFERENCES

1. HENCH, P. S., VANZANT, F. R., and NOMLAND, R.: Basis for the early differential diagnosis of gout: a clinical comparison of 100 cases each of rheumatic fever, infectious arthritis and gout, Collected Papers of the Mayo Clinic and Mayo Foundation, 1928 xx, 790.
2. LOCKIE, L. M., and HUBBARD, R. S.: Gout: changes in symptoms and purine metabolism produced by high fat diets in four gouty patients, Jr. Am. Med. Assoc., 1935, civ, 2072.
3. HARDING, V. J., ALLEN, K. D., EAGLES, B. A., and VAN WYCK, H. B.: The effect of high fat diets on the content of uric acid in the blood, Jr. Biol. Chem., 1925, lxiii, 37.
4. LENNOX, W. G.: Increase of uric acid in the blood during prolonged starvation, Jr. Am. Med. Assoc., 1924, lxxxii, 602.

A STATISTICAL STUDY OF ALLERGY IN ARTHRITIS *

By Eugene F. Traut, M.D., and Emil G. Vrtiak, M.D.,†
Chicago, Illinois

Because of the similarity of certain aspects of rheumatic fever to serum sickness, the classical example of allergy, we investigated the frequency of asthma, hay fever, urticaria, eczema, migraine, and hyperesthetic rhinitis in 459 victims of the rheumatic state, in the Central Free Dispensary, in Cook County Hospital, Chicago, Illinois, and in private practice. These individuals, living under identical conditions and with foci inhabited by bacteria common to all, have responded with clinical rheumatism to infections, injuries, fatigue or to dietary inadequacies. That these individuals should react with rheumatism to environmental influences apparently identical with those affecting the non-rheumatic population has been said to be due to allergy or hypersensitiveness.[1, 2] Even gout has been called an expression of hypersensitiveness to food.[3]

As in the case of Koch's early demonstration in the tuberculin reaction of hypersensitiveness to derivatives of tubercle bacilli, Swift and others have demonstrated hypersensitiveness to other bacterial products. Touart and Thomas [4] added further evidence of the allergic nature of skin reactions to bacterial products by their demonstration of eosinophiles at the sites of injection. Swift [5, 6, 7] and his co-workers and Birkhaug [8] have made animals hypersensitive to the products of non-hemolytic, as well as green or hemolytic streptococci, and again desensitized them. Miller [9] made rabbits hypersensitive to gonococci. Pilot [10] secured positive skin tests with a filtrate of *Staphylococcus aureus* in patients infected with this organism. Mackenzie and Hanger [11] made human beings hypersensitive to the supernatant fluid of streptococcus cultures. Swift's work indicated that foci of infection played a sensitizing rôle.[12] Swift,[5, 12, 13] Derick,[14] I,[15] and others [16] have found rheumatic individuals hypersensitive to streptococci as judged by skin tests. According to Brown [17] the possibility of food or bacterial allergy should be considered in every case of arthritis. He and others [18] perform skin tests with bacteria and use elimination diets to find the offending agent in arthritis. Harkavy and Hebald [19] report nine instances of arthritis in asthmatics. In eight of these patients the removal of foci relieved the arthritis while simultaneously improving the asthma. According to their presumptions, both syndromes were an expression of hypersensitiveness to the bacteria inhabiting the foci.

* Received for publication December 28, 1937.
From the John McCormick Institute for Infectious Diseases and the Arthritis Clinic of the Central Free Dispensary, Rush Medical College, Chicago, Illinois.
† Deceased.

The conditions noted as occurring in the antecedents of patients with the rheumatic complex belong in that more specific sub-group of allergic states called atopic. In associating certain arthropathies with allergy, we are not specifying bacterial, food, or physical allergy. "Bacterial allergy, as indicated by the indurative skin test, is apparently very different from atopy, which is an hereditary condition and whose expression of allergy is edema. To be sure, under certain circumstances there is a relationship between these two expressions of human hypersensitiveness, but certainly they are not interchangeable." [20]

The relation of arthritis to allergy may be, as Pilot [21] has suggested, simply that arthritis, especially of the rheumatoid type, and allergic disease tend to occur in certain labile individuals who react excessively to changes in their environment. Arthritis and allergic symptoms tend to occur in these individuals in whom allergic and arthritic manifestations can be said to have a meeting ground. Rackemann doubts that arthritis can be placed in the same category as asthma, hay fever, eczema or urticaria. His asthma and hay fever patients have rarely had any rheumatic complaints.[22] With allergy playing a rôle in rheumatism, the rheumatic population might be composed of a large or preponderant number of individuals having also asthma, hay fever, urticaria, eczema or possibly even migraine or hyperesthetic rhinitis.

Methods and Findings

Four hundred fifty-nine patients in the Central Free Dispensary, in the Cook County Hospital and in our private practices were questioned by the same personnel regarding the occurrence, the frequency of such occurrence, and the severity of asthma, hay fever, urticaria and eczema, either in themselves, one or both parents, blood aunts or uncles and in one or both grandparents. Because of the alleged allergic association of migraine [31] and of hypertrophic rhinitis, as manifested by catarrh, obstructed nose and repeated colds,[24] patients were cross-examined for these syndromes. Of these, 359 had rheumatic heart disease, atrophic or hypertrophic arthritis as defined by the American Association for the Study and Control of Rheumatic Diseases, and 100 others (a non-rheumatic group) were chosen at random from the general sick population. We chose these 100 "controls" from sick people to secure a view of allergy's effect in its relation to rheumatism as contrasted with its relation to illness in general.

Allergy in Non-Rheumatic Patients

A report of the questioning of these people, sick with a variety of illnesses not rheumatic, forms the basis of our evaluation of the frequency or intensity of allergy in the rheumatic patients. Of these non-rheumatic sick, 3 per cent were afflicted with asthma or hay fever, 2 per cent being asthmatic and 1 per cent admitting hay fever; 13 per cent had had "hives." We feel

that their report of urticarial symptoms is reliable. That 5 per cent of the patients had eczema is open to more question; possibly various cutaneous mycoses would be reported under this heading. However, even in the fungus diseases of the skin, allergy may play a part. It has been our own observation that itching and the size of the fungus growth are usually greater and more persistent in allergic patients. Thus, 19 per cent of our control group are allergic as judged by their being sufferers from asthma, hay fever, urticaria or eczema. A patient having more than one of the allergic syndromes was counted as one person showing allergy. In other words, a patient with urticaria and hay fever was counted as one instance of allergy, the severity and frequency of his allergic manifestations being noted.

Type of Cases	No. of Cases	Percentage of Patients Having								Percentage Having Family History of	
		Asthma	Hay fever	Urticaria	Eczema	Rhinitis	Migraine	Asthma, Hay Fever, Urticaria, Eczema	Asthma Hay fever Urticaria Eczema Rhinitis Migraine	Asthma Hay fever Urticaria Eczema	Asthma Hay fever Urticaria Eczema Rhinitis Migraine
Atrophic Arthritis.....	175	5.2	12.6	20.6	8.0	25.1	36.2	18.8	54.1	10.9	12.0
Hypertrophic Arthritis....	129	7.8	16.2	23.2	10.8	37.9	34.8	30.2	61.2	13.9	13.9
Rheumatic Heart Disease.....	55	7.2	10.9	21.8	1.8	Not	questioned	30.9	Not questioned	29.1	Not questioned
Controls.....	100	2.0	1.0	13.0	5.0	14.0	18.0	19.0	37.0	10.0	11.0

Eighteen per cent of this non-rheumatic control group had had sick headaches. The question as to the allergic etiology of all migraine is still debatable. These patients are not to be excluded from the allergic group, even if the sick headache were released by an emotional upset or refractive error. The probability of an allergic constitution is still strong.[25, 26, 27, 28]

Fourteen per cent of these controls complained of frequent colds, nasal catarrh or stuffy noses. Anatomical deformities of the nasal passages and acute upper respiratory infections were excluded as far as possible. It was assumed, on admittedly debatable grounds, that these symptoms indicated nasopharyngeal hypersensitiveness or hypertrophic rhinitis.

To include migraine and these nasal disturbances would raise the allergic percentage of our controls to 37 per cent.

Eleven per cent of these non-arthritic controls recalled near blood relatives with asthma (6 per cent), eczema (4 per cent), hay fever (2 per cent) and colds and catarrh (1 per cent). Strangely enough, none of them re-

membered any relatives with sick headaches. Such an impressive syndrome as asthma would be calculated to impress itself on their memory. Among such asthmatics there may have been instances of non-allergic cardiac decompensation or, less likely of tuberculosis with dyspnea.

According to expectations, the allergic controls had a higher incidence of familial hypersensitiveness (21 per cent). This was exclusive of migraine and "colds," and is to be contrasted with the 11 per cent of the whole control group admitting allergic disease in their families. The control group complained most frequently of colds and catarrh. Migraine was their next most common "evidence of allergy." Urticaria was more common than eczema, asthma and hay fever combined.

Allergy in the Rheumatic Group

According to the patients' stories, allergic manifestations were much more prominent (30.9 per cent) in the 55 patients with rheumatic heart disease. This agrees with the commonly observed similarity of some cases of rheumatic fever and serum disease. The relation of the various expressions of hypersensitiveness persists in this cardiac group, hives being the most common (21.8 per cent). Eighteen per cent of the patients have had either asthma or hay fever. This is a frequency six times as great as that observed in the controls. As contrasted with the relatives of the control patients, more of the patients with rheumatic hearts have a family history of allergy (29.1 per cent). The patients with rheumatic heart disease were not questioned regarding migraine or "colds."

A similarly high incidence of allergic disease was found in that group of chronic rheumatics including hypertrophic (osteo-arthritic) arthritis. The common difficulty in clearly separating the two great groups of chronic arthritics was experienced. Admittedly most of the patients in that group termed hypertrophic and many in the atrophic group could more properly be called "mixed." They were assigned to either file, depending upon a preponderance of those constitutional peculiarities and disease manifestations characteristic of the two great groups. Of the 129 patients with hypertrophic arthritis, 30.2 per cent had had asthma, hay fever, urticaria or eczema. Fewer gave a history of allergy in the family than was the case with rheumatic heart disease. The incidence of migraine in patients with hypertrophic arthritis was almost twice as great as in the controls: 34.8 per cent as compared with 18 per cent.

Contrary to our anticipations, of all the rheumatic syndromes studied, allergic manifestations were least common in atrophic arthritis (chronic infectious, rheumatoid arthritis, arthritis deformans). This atrophic group of the chronic arthritics reported an increased susceptibility to colds as manifested by attacks of coryza. This group also had migraine twice as commonly as the controls. This might be anticipated from Stieglitz's description [30] of the migrainous constitution. On the other hand, the chronic

arthritics of the opposite or sthenic constitution admitted a similarly high incidence of migraine. Headaches ascribable to the radiculitis consequent upon arthritis of the cervical vertebrae were eliminated as far as possible. Of all the complaints considered, migraine was that most commonly elicited from the entire rheumatic group. Colds and catarrh were next in frequency. As in the controls, hives were much more common than hay fever, asthma or eczema.

Summary

So far as the degree of allergy in a patient or his family is concerned, as estimated by the number of allergic diseases or the frequency and severity of their occurrence in a given patient, or by the closeness and number of allergic relatives, all of the rheumatic groups show from two to three times as much allergy as the controls.

The rheumatic patients exceeded the controls by 200 to 300 per cent in the frequency and severity of the various manifestations of allergy in themselves as well as in the closeness of relationship of allergic relatives.

Discussion

The patient with any of the commonly accepted evidences of past or present rheumatism is distinguished from the rest of the population by his distinctive reactions to bacterial invasion, as well as to climatic changes. The rheumatic is further peculiar in that disturbance of his so-called focal infections, for example by surgery, frequently provokes an aggravation of his illness. His behavior simulates that of the anaphylactic or hypersensitive state. He reacts distinctively to skin tests with bacterial proteins. In addition, the high incidence of allergic manifestations in people with rheumatism is evidence of an increased tendency of the rheumatic to react in an unusual manner (or be hypersensitive) to his environment.

Rackemann estimates the incidence of hypersensitiveness in the general population, as manifested by asthma and hay fever, to be between 0.5 per cent and 1.0 per cent.[22] Vaughan [23] believes in an incidence of allergy of 10 per cent in the total population. Of our 100 sick people 3 per cent had asthma or hay fever and 19 per cent had or had had either asthma, hay fever, urticaria or eczema. To include migraine and hypertrophic rhinitis as evidences of allergy would lead to the conclusions that 37 per cent of our general sick population are allergic. The tendency to call upon allergy to explain many and various illnesses not frankly or solely of allergic origin is prevalent. In spite of the tendency of some [29, 17] to assume an allergic relationship for rheumatoid arthritis and indeed to practice allergic methods in its diagnosis and treatment we found no more evidence of hypersensitiveness in rheumatoid arthritis than in non-rheumatic sick people.

Conclusions

1. Rheumatic patients have allergic diseases much more commonly than the general sick population.

2. Blood relatives of rheumatics have more allergic disease than the general sick population.

3. Migraine is the most frequent allergic manifestation of all sick people interrogated.

4. Migraine is the most common allergic manifestation of rheumatic patients.

5. Urticaria is more common than asthma, hay fever or eczema in the 459 people questioned.

6. Urticaria is more common than asthma, hay fever or eczema in rheumatic patients.

7. Patients with atrophic arthritis showed less evidence of hypersensitiveness than did the patients with hypertrophic arthritis, or those with a history of previous rheumatic fever.

BIBLIOGRAPHY

1. Swift, H. F.: Rheumatic fever, Nelson's loose leaf living medicine, Thomas Nelson & Son, New York City, Volume 1, 1920, Chapter 2, pp. 31–48.
2. Post, W. E.: Focal infection, ibid.
3. Gudzent, F.: Testing and treatment of rheumatism and gout with specific allergens, Deutsch. med. Wchnschr., 1935, lxi, 901.
4. Touart, M.D., and Thomas, W. S.: Eosinophilia in bacterial reaction sites, New York State Jr. Med., 1933, xxxiii, 1.
5. Hitchcock, C. H., and Swift, H. F.: Studies on indifferent streptococci, Jr. Exper. Med., 1929, xlix, 637.
6. Hitchcock, C. H., Camero, A. R., and Swift, H. F.: Perivascular reactions in lung and liver following intravenous injection of streptococci into previously sensitized animals, Jr. Exper. Med., 1934, xlix, 283.
7. Schultz, M. P., and Swift, H. F.: Reactions of rabbits to streptococci (comparative sensitizing effect of intracutaneous and intravenous inocula in minute doses), Jr. Exper. Med., 1932, lv, 505.
8. Birkhaug, K.: Allergic reactions with a toxin-producing strain of the non-methemoglobin-forming streptococcus isolated from rheumatic fever, Jr. Infect. Dis., 1928, xliii, 280.
9. Miller, P.: Some observations on the specificity of allergic reactions to certain of the gram-negative diplococci, Trans. Assoc. Am. Phys., 1933, xlviii, 382.
10. Pilot, I.: Discussion of skin reactions with *Staphylococcus aureus*, Jr. Am. Med. Assoc., 1931, xcvii, 878.
11. Mackenzie, G. M., and Hanger, F. M.: A study of hypersensitiveness to derivatives of hemolytic and non-hemolytic streptococci, Proc. Soc. Exper. Biol. and Med., 1923, xxi, 442.
12. Swift, H. F., Derick, C. L., and Hitchcock, C. H.: Bacterial allergy (hyperergy) to non-hemolytic streptococci in its relation to rheumatic fever, Jr. Am. Med. Assoc., 1928, xc, 907.
13. Swift, H. F., Hitchcock, C. H., Derick, C. L., and McEwen, C.: Intravenous vaccination with streptococci in rheumatic fever, Am. Jr. Med. Sci., 1931, clxxxi, 1.

14. Derick, C. L., and Fulton, M. N.: Skin reactions of patients and normal individuals to protein extracts of streptococci, Jr. Clin. Invest., 1931, x, 1.
15. Traut, E. F.: Skin tests with bacterial products in arthritic and non-arthritic individuals, Jr. Allergy, 1937, viii, 501.
16. Gibson, H. J., Thomson, W. A. R., and Stewart, D.: Hemolytic streptococcus as factor in causation of acute rheumatism, Arch. Dis. Child., 1933, viii, 1.
17. Brown, G. T.: Allergic phases of arthritis, Jr. Lab. and Clin. Med., 1934, xx, 247.
18. Turnbull, J. A.: The relation of anaphylactic diseases to arthritis, Jr. Am. Med. Assoc., 1924, lxxxii, 1757.
19. Harkavy, J., and Hebald, S.: Quoted by Brown.[17]
20. Alexander, Henry L.: Personal communication.
21. Pilot, I.: Personal communication.
22. Rackemann, F. M.: The rôle of allergy in arthritis, New England Jr. Med., 1933, ccviii, 1347.
23. Vaughan, W. T.: Allergy, 1934, C. V. Mosby Company, St. Louis, p. 68.
24. Harkavy, J.: Allergic manifestations of the common cold, Med. Clin. North Am., 1933, xvii, 193.
25. Rackemann, F.: Clinical allergy, 1931, Macmillan Company, New York, p. 133.
26. Balyeat, R. M., and Rinkel, H. J.: Studies in allergic migraine, Ann. Int. Med., 1931, v, 713.
27. DeGowin, E.: Allergic migraine, Jr. Allergy, 1932, iii, 447.
28. Rinkel, H. J.: Migraine. Some considerations of allergy as a factor in familial recurrent headache, Jr. Allergy, 1933, iv, 303.
29. Dorst, S. E., and Wherry, W. B.: Local skin reactions in the selection of antigens for autogenous vaccines, Ohio State Med. Jr., 1928, xxiv, 539.
30. Stieglitz, E. J.: Migraine physique, Am. Jr. Med. Sci., 1935, clxxxix, 359.
31. Vaughan, W. T.: Allergy, 1934, C. V. Mosby Company, St. Louis, p. 336.

ACTIVE IMMUNIZATION AGAINST TETANUS*

By HERMAN GOLD, M.D., *Chester, Pa.*

ACTIVE immunization against tetanus has aroused a great deal of interest among clinicians and public health workers because of its possible use as a preventive measure of general applicability. The antitoxin titer produced by the injection of tetanus toxoid, and the influence exerted upon this titer by such factors as dosage, time interval between injections, associated antigens and "repeat" or stimulating injection of toxoid, have been the subject of careful investigation.[1-32] We now wish to add our findings on the comparative value of various antigenic preparations.

Tetanus toxoid (plain) (No. 5969), *tetanus toxoid (plain)* to which 0.4 per cent alum was added (No. 5969–5) and *alum precipitated tetanus toxoid (refined)* (No. 8387–3) were used for active immunization of 32 healthy individuals, 14 to 28 years of age.

Twelve persons (group A) † were immunized by means of three 1.0 c.c. injections of *tetanus toxoid plain* (No. 5969). The period between injections was varied in order to determine the interval of time that will give the best antitoxin response (chart 1). This appears to be one month.

When 0.5 c.c. of the plain toxoid used in this series was injected into a group of guinea pigs, it produced at the end of six weeks 0.1 unit of antitoxin per c.c. of pooled blood serum obtained from three animals. Injection of 1.0 c.c. produced a little more than 0.5 unit per c.c. of the pooled blood serum of four guinea pigs.

Our subjects showed 0.003 unit or less of antitoxin per c.c. of blood serum before active immunization was instituted. Eighteen to 32 days after the final dose was given all subjects but one showed 0.1 to 2.0 units of antitoxin per c.c. of blood serum. The exception (case 9963) showed 0.01 unit, but when tested 59 days after the third dose he had 0.25 unit. Two individuals dropped to less than 0.1 unit when retested 105 days after immunization. One of them (case 9972), when tested again three months later, showed 0.1 unit but dropped to less than 0.1 unit on subsequent tests. The same variation occurred in case 9963. This apparent discrepancy may be due to actual changes in the antitoxin content of the blood or to variation inherent to the biologic assay used. Of the subjects tested six months after immunization three persons or 27.3 per cent showed less than 0.1 unit. The rest had 0.1 unit or more. Three months later seven subjects, or 58.3 per cent of the tested individuals, had less than 0.1 unit. At the end of one year, two subjects showed 0.25 unit, while seven tested less than 0.1 unit.

* Received for publication February 28, 1939.

† We wish to thank Dr. E. A. Whitney, Medical Director of The Elwyn Training School, Elwyn, Pa., for allowing us to use inmates of this institution for this study. All antigens and tests reported in this paper were obtained from, and performed by, the Technical Division, Mulford Biological Laboratories, Sharp and Dohme, Glenolden, Pa.

CHART I

GROUP A

TETANUS TOXOID PLAIN 5969

Basic Course of Immunization: Three Doses 1.0 c.c. each.

Titer expressed in units of tetanus antitoxin per cubic centimeter of blood serum

Case	Control Titer	Interval Between 1st and 2nd Dose	Interval Between 2nd and 3rd Dose	Days After Third Dose Titer							
9960	0.003	31 days	28 days	32 days 0.50	91 days 0.25	182 days +0.25 −0.50	276 days +0.10 −0.25	370 days 0.25	461 days 0.25	657 days 0.10	748 days 0.1
9964	−0.003	31 days	28 days	32 days +1.0 −2.0	91 days +0.25 −1.0	182 days 0.25	276 days +0.10 −0.25	370 days +0.01 −0.10	461 days +0.01 −0.10	—	—
9966*	−0.003	31 days	28 days	32 days 0.25	91 days 0.10	182 days +0.01 −0.10	276 days +0.01 −0.10	370 days +0.01 −0.10	—	—	—
9968*	−0.003	31 days	14 days	28 days 0.10	105 days +0.01 −0.10	196 days +0.01 −0.10	290 days +0.01 −0.10	384 days +0.01 −0.10	—	—	—
9972	−0.003	31 days	14 days	28 days 0.10	105 days +0.01 −0.10	196 days 0.10	290 days +0.01 −0.10	—	—	—	—
9986*	−0.003	31 days	14 days	28 days 0.25	105 days +0.10 −0.25	196 days 0.10	290 days +0.01 −0.10	384 days +0.01 −0.10	—	—	—

* Received a "repeat injection."

CHART I—*Continued*

Case	Control Titer	Interval Between 1st and 2nd Dose	Interval Between 2nd and 3rd Dose	Days After Third Dose Titer							
9970	- 0.003	31 days	14 days	28 days +0.10 −0.25	105 days +0.10 −0.25	196 days +0.10 −0.25	290 days 0.10	384 days +0.01 −0.10	475 days +0.01 −0.10	—	—
9963*	−0.003	31 days	15 days	27 days 0.01	59 days 0.25	105 days +0.01 −0.10	195 days 0.50	289 days 0.01	383 days +0.01 −0.10	—	--
9962*	−0.003	46 days	27 days	32 days 0.50	88 days 0.10	168 days —	262 days +0.01 −0.10	356 days +0.01 --0.10	—	—	—
9961	0.003	46 days	27 days	32 days 0.50	88 days 0.25	168 days +0.10 −0.25	272 days ÷0.10 −0.25	—	453 days 0.25	—	—
9969	−0.003	59 days	14 days	18 days +2.0 −3.0	88 days 0.50	168 days +0.25 −0.50	262 days 0.25	356 days 0.25	447 days +0.10 −0.25	643 days +0.10 −0.25	734 days 0.10
9967	−0.003	59 days	14 days	18 days 0.25	88 days 0.10	168 days +0.01 −0.10	262 days +0.01 −0.10	—	—	—	—

* Received a "repeat injection."

When retested 25 months after the basic course of immunization was completed, cases 9960 and 9969 still showed 0.10 unit per c.c. of blood serum.

Five members of this group A received a fourth or " repeat " dose of the same toxoid one year after the basic course of immunization had been completed (chart 2). At this time their antitoxin titer had fallen to + 0.01 — 0.1 unit. When tested four days after the administration of the " repeat " dose, two subjects showed no change in titer, whereas three had increased to 0.1 unit or more. On the fifth day, all subjects showed good protection. The titer for the entire group ranged above 2.0 units per c.c. of blood serum one month after the stimulating dose was given. At the end of 16 months, there was a considerable drop in the antitoxin titer of the group, although it was still well above the minimum protective level of 0.1 unit.

A second group (B) of 12 young people received treatment similar to that given the members of Group A except that the antigen used consisted of the *tetanus toxoid plain* (No. 5969) to which 0.4 per cent alum had been added (chart 3).

The injection of 0.5 c.c. of this mixture of plain toxoid and of 0.4 per cent alum (No. 5969–5) into a group of eight standard guinea pigs resulted at the end of six weeks in the production of 2.0 units of antitoxin per c.c. of pooled blood serum. A similar titer was obtained following the injection of 1.0 c.c. of this antigen.

Before immunization, the control titer of our subjects was less than 0.003 unit. Eighteen to 46 days after the last dose of toxoid was given, all but one subject had more than 0.10 unit per c.c. of blood serum. The exception, case 9975, who had 0.10 unit, dropped to + 0.01 — 0.10 unit when retested 104 days after the last dose of toxoid. When the group was retested 168 to 196 days after immunization, it was found that two additional individuals had dropped to — 0.10 unit. Three months later another two subjects showed — 0.10 unit, and at the end of one year six out of 10 patients tested showed — 0.10 unit. The rest had 0.10 to 0.25 unit of antitoxin per c.c. of blood serum. When these four subjects were retested 22 months after the basic course of immunization was completed, one showed + 0.01 — 0.10 unit while the other three had a good protective titer of 0.1 unit or more. Three months later, case 9981 dropped to — 0.1 unit while two subjects, cases 9979 and 9976, showed + 0.10 — 0.25 and 0.50 unit respectively.

Four members of this Group B received a fourth " repeat " dose of 1.0 c.c. of plain toxoid plus alum (No. 5969–5) one year after the basic course of immunization had been completed (chart 4). The control titer before the " repeat " injection was + 0.01 — 0.10 unit. Four days later, only one subject showed 0.10 unit. The rest had — 0.10 unit. On the fifth day, all but one subject had 0.10 to 0.25 unit. The exception still showed the control values of + 0.01 — 0.10 unit. When retested on the seventh day, this subject had 1.0 unit. The entire group, with the exception of one

CHART II

GROUP A

TETANUS TOXOID PLAIN 5969

"Repeat" (Fourth) Dose (1.0 c.c.)

Titer expressed in units of tetanus antitoxin per c.c. of blood serum

Case	Days After 3rd Dose Titer	Interval Between 3rd and 4th Dose	Days After "Repeat" (Fourth) Dose Titer								
			4 Days	5 Days	7 Days	29 Days	91 Days	196 Days	287 Days	378 Days	474 Days
9966	370 days +0.01 −0.10	370 days	+0.01 −0.10	0.10	+0.25 −0.50	+2.0 −3.5	1.0	+0.50 −1.0	0.50	0.50	
9963	383 days +0.01 −0.10	383 days	+0.01 −0.10	+0.10 −0.25	+1.0 −2.0	2.0	2.0	2.0	+0.50 −1.0	0.50	0.50
9986	384 days +0.01 −0.10	384 days	+0.10 −0.25	+0.50 −1.0	3.5	+3.0 −5.0	+1.0 −3.0	+0.50 −0.75	+0.50 −0.75	0.25	+0.10 −0.25
9968	384 days +0.01 −0.10	384 days	0.10	0.25	+1.0 −2.0	+3.0 −5.0	+1.0 −3.0	+0.50 −1.0	+0.50 −1.0	0.50	+0.25 −0.50
9962	356 days +0.01 −0.10	356 days	0.10	0.25	+1.0 −3.0	+1.0 −3.0	+0.50 −1.0	+0.25 −0.50	+0.25 −0.50	+0.25 −0.50	0.25

CHART III

GROUP B

TETANUS TOXOID PLUS ALUM 5969–5

Basic Course of Immunization: Three doses 1.0 c.c. each.

Titer expressed in units of tetanus antitoxin per cubic centimeter of blood serum

Case	Control Titer	Interval Between 1st and 2nd Dose	Interval Between 2nd and 3rd Dose	Days After Third Dose Titer								
9977	−0.003	46 days	27 days	32 days +0.25 −1.0	88 days +0.25 −0.50	168 days +0.25 −0.50	—	—	—	—	—	—
9983*	0.003	45 days	28 days	18 days 0.50	88 days 0.10	168 days +0.10 −0.25	262 days +0.01 −0.10	356 days +0.01 −0.10	—	—	—	—
9985*	−0.003	45 days	28 days	32 days 0.50	88 days 0.10	168 days +0.01 −0.10	262 days +0.01 −0.10	356 days +0.01 −0.10	—	—	—	—
9978*	−0.003	31 days	42 days	32 days 0.25	88 days +0.01 −0.10	168 days +0.01 −0.10	262 days +0.01 −0.10	356 days +0.01 −0.10	—	—	—	—
9979	−0.003	31 days	28 days	46 days +0.25 −1.0	91 days 0.25	182 days +0.10 −0.25	276 days +0.10 −0.25	370 days 0.10	461 days 0.10	566 days +0.10 −0.25	657 days +0.10 −0.25	748 days +0.10 −0.25
9976	−0.003	31 days	28 days	32 days +1.0 −3.0	91 days +1.0 −2.0	182 days +0.5 −1.0	276 days +0.25 −0.50	370 days +0.25 −0.50	461 days +0.25 −0.50	566 days +0.25 −0.50	657 days +0.25 −0.50	748 days 0.50

* Received repeat (fourth) dose.

CHART III—*Continued*

Case	Control Titer	Interval Between 1st and 2nd Dose	Interval Between 2nd and 3rd Dose	Days After Third Dose Titer								
9974	−0.003	31 days	28 days	46 days 0.25	91 days 0.10	182 days 0.10	276 days +0.01 −0.10	—	—	—	—	—
9975*	−0.003	31 days	15 days	27 days 0.10	104 days +0.01 −0.10	195 days +0.01 −0.10	289 days +0.01 −0.10	383 days +0.01 −0.10	—	—	—	—
9973	−0.003	31 days	15 days	27 days +0.10 −0.25	104 days +0.10 −0.25	195 days 0.10	289 days 0.10	383 days +0.01 −0.10	474 days +0.01 −0.10	—	—	—
9982	−0.003	31 days	14 days	28 days +0.25	105 days +0.25 −0.50	196 days +0.25 −0.50	290 days 0.10	384 days +0.01 −0.10	475 days +0.01 −0.10	—	—	—
9981	−0.003	31 days	14 days	28 days +0.25	105 days +0.25 −0.50	196 days 0.25	290 days +0.10 −0.25	384 days +0.10 −0.25	475 days 0.10	580 days 0.10	671 days 0.10	762 days +0.01 −0.10
9984	−0.003	31 days	14 days	32 days +0.25	105 days +0.25 −0.50	196 days +0.25 −0.50	290 days 0.25	384 days +0.10 −0.25	475 days +0.10 −0.25	580 days 0.10	671 days +0.01 −0.10	

* Received repeat (fourth) dose.

CHART IV

GROUP B

TETANUS TOXOID PLUS ALUM 5969–5

"Repeat" (Fourth) Dose (1.0 c.c.)

Titer expressed in units of tetanus antitoxin per c.c. of blood serum

Case	Days After 3rd Dose Titer	Interval Between 3rd and 4th Dose	Days After "Repeat" (Fourth) Dose Titer								
			4 Days	5 Days	7 Days	29 Days	91 Days	196 Days	287 Days	378 Days	474 Days
9975	383 days +0.01 −0.10	383 days	+0.01 −0.10	+0.10 −0.25	1.0	+0.5 −1.0	+0.25 −0.5	+0.25 −0.5	+0.10 −0.25	0.10	0.10
9978	356 days +0.01 −0.10	356 days	+0.01 −0.10	0.25	3.0	+3.5 −5.0	+1.0 −3.0	0.75	0.25	0.25	+0.10 −0.25
9985	356 days +0.01 −0.10	356 days	+0.01 −0.10	+0.01 −0.10	1.0	+1.0 −3.0	0.50	+0.25 −0.5	+0.10 −0.25	+0.10 −0.25	0.10
9983	356 days +0.01 −0.10	356 days	0.10	+0.10 −0.25	+1.0 −2.0	2.0	+0.50 −1.0	1.0	0.50	0.50	+0.25 −0.50

member, showed a further increase in the titer when retested 29 days after the repeat dose was given. At the end of three months, all the patients showed a drop in titer. However, the antitoxin content of the blood was still well above the minimum protective level of 0.1 unit per c.c. When retested 16 months after the " repeat " injection all four subjects showed 0.10 unit or more of tetanus antitoxin per c.c. of blood serum.

Eight young men (Group C) were immunized with two doses of *tetanus toxoid alum precipitated (refined)* (No. 8387–3). Half of the group received 0.5 c.c., whereas the other half got 1.0 c.c. at each injection. The two doses were given 146 days apart (chart 5).

When 0.5 c.c. of the toxoid used in this series was injected into a group of standard guinea pigs, there developed at the end of six weeks, five units of tetanus antitoxin per c.c. of pooled blood serum obtained from four animals. At the end of 12 weeks, two guinea pigs tested a little more than 3.0 units, whereas at the end of 25 weeks, tests on a surviving animal still showed a little more than 1.5 unit per c.c. of blood serum. The injection of a 1.0 c.c. dose of this alum toxoid produced at the end of six weeks 5.0 units of antitoxin per c.c. of pooled serum obtained from six guinea pigs. At the end of 12 weeks, the pooled serum of four pigs showed 9.0 units. At the end of 18 weeks the serum pooled from three animals showed 8.0 units, whereas at the end of 25 weeks after injection of the alum toxoid, one surviving guinea pig showed 4.0 units.

The control bleeding of our subjects before immunization showed — 0.003 unit of tetanus antitoxin. When tested 31 days after the second dose, all the members of the group had a good protective level of antitoxin titer in their blood, ranging from 0.25 to 7.0 units (chart 5). Little can be said concerning the effect of dosage upon the antitoxin titer in this small series of cases, since both the lowest and the highest values for the entire group occurred in those individuals that received the 0.5 c.c. dose. Two members of the 0.5 c.c. group showed the same titer as in the 1.0 c.c. group. When tested 90 days after the second injection of toxoid, one subject (case 10005), who on previous testing had shown the lowest value in the group, dropped to 0.01 unit. The rest still had a good protective titer. Two subjects that received the 1.0 c.c. dose also showed less than 0.10 unit when tested two months later. In other words, 43 per cent of the individuals tested five months after immunization was completed showed less than the amount of antitoxin necessary for protection. On the other hand, three members of the group showed 0.1 unit or more when tested 371 days after the second injection of toxoid. One of these subjects dropped to — 0.1 unit when retested 18 months after immunization. The other two subjects (cases 10006 and 10013) still showed 0.1 and 0.25 units respectively when tested about two years after the second dose of toxoid.

Three members of this group received a third or " repeat " injection of 1.0 c.c. of the same toxoid 237 days after the second dose, when the antitoxin level of their blood was less than 0.1 unit (chart 6). Four days after

CHART V

GROUP C

TETANUS TOXOID, ALUM PRECIPITATED, REFINED 8387-3

Two Doses Given 146 Days Apart.

Titer expressed in units of tetanus antitoxin per c.c. of blood serum

Case	Control Titer	First Dose	Interval Between 1st and 2nd Dose	Second Dose	Days After Second Dose Titer								
					31 Days	90 Days	150 Days	237 Days	269 Days	371 Days	524 Days	615 Days	711 Days
10005*	−0.003	0.5 c.c.	146 days	0.5 c.c.	0.25	0.01	+0.01 −0.10	0.01	—	—	—	—	—
10006	−0.003	0.5 c.c.	146 days	0.5 c.c.	7.0	+1.0 −3.0	1.0	—	1.0	0.5	0.5	+0.25 −0.50	0.25
10011	0.003	0.5 c.c.	146 days	0.5 c.c.	0.75	—	—	—	—	—	—	—	—
10013	−0.003	0.5 c.c.	146 days	0.5 c.c.	3.0	+0.5 −1.0	+0.25 −0.50	—	—	0.25	0.10	0.10	0.10
10007	−0.003	1.0 c.c.	146 days	1.0 c.c.	+1.0 −2.0	0.50	0.25	—	0.10	0.10	+0.01 −0.10	—	—
10008*	0.003	1.0 c.c.	146 days	1.0 c.c.	+1.0 −3.0	+0.10 −0.25	+0.01 −0.10	0.01	—	—	—	—	—
10010	−0.003	1.0 c.c.	146 days	1.0 c.c.	3.0	+0.5 −1.0	0.50	—	0.25	—	—	—	—
10012*	−0.003	1.0 c.c.	146 days	1.0 c.c.	+0.5 −1.0	0.10	+0.01 −0.10	+0.01 −0.10	—	—	—	—	—

* Received a "repeat" (third dose).

CHART VI

GROUP C

TETANUS TOXOID, ALUM PRECIPITATED, REFINED 8387–3

Antitoxin Titer Following Injection of a "Repeat" (Third) 1.0 c.c. Dose.

Titer expressed in units of tetanus antitoxin per c.c. of blood serum

Case	Titer Before Third Dose	Interval Between 2nd and 3rd Dose	Days After Third Dose Titer									
			4 Days	5 Days	6 Days	7 Days	29 Days	91 Days	196 Days	295 Days	386 Days	482 Days
10005	0.01	237 days	+0.01 −0.10	—	—	+1.0 −3.0	+1.0 −2.0	0.50	0.25	0.25	+0.10 −0.25	0.10
10008	0.01	237 days	+0.01 −0.10	—	+0.25 −0.50	+1.0 −2.0	1.0	+0.50 −1.0	0.25	+0.10 −0.25	0.10	0.10
10012	+0.01 −0.10	237 days	+0.01 −0.10	0.25	—	+1.0 −3.0	+3.0 −5.0	+1.0 −3.0	1.0	0.50	+0.25 −0.50	0.25

the " repeat " injection, they still showed less than 0.10 unit. On the fifth day, case 10012 had 0.25 unit. On the seventh day, all three subjects had more than 1.0 unit, an increase of over 100 per cent. A month after injection of the stimulating dose two subjects showed a decrease, whereas one member showed a considerable increase in the antitoxic titer of their blood. Good protection of 0.1 unit or more was still maintained 16 months later.

Discussion

The injection of tetanus toxoid produces in most individuals a slight to moderate local reaction that lasts one to three days. No systemic reactions were encountered. The alum precipitated toxoid tends to produce a subcutaneous nodule at the site of injection similar to that produced by diphtheria alum toxoid. It is usually absorbed in two to four weeks.

The results obtained in the series of cases immunized with the plain toxoid compare favorably with those already reported in the literature.[3, 4, 5, 7, 10, 11, 14] The subjects immunized with the plain toxoid plus 0.4 per cent alum, seemed to do a bit better than those injected with the plain antigen. However, the number of subjects is small and the differences noted are not clear cut enough to permit of any definite conclusions.

In agreement with Jones and Moss,[14] we found that, within the limitations of the schedule (dose and time interval) used by us, two doses of alum precipitated toxoid produced a higher level of antitoxic immunity than three injections of plain toxoid or plain toxoid plus 0.4 per cent alum. The loss of antitoxin in all groups, regardless of the type of antigen used, was most marked in the first few months following the basic course of immunization, so that by the end of nine months to a year, the great majority of the immunized individuals showed less than the minimum protective level of 0.1 unit of antitoxin per c.c. of blood serum. Although the amount of antitoxin produced and lost varies in different individuals and is actually unpredictable, and though the loss in titer is not directly proportionate to the amount of antitoxin previously present in the blood, there is a definite tendency on the part of those subjects that develop the highest values of antitoxin to retain a protective titer for a longer period of time.

The first dose of alum precipitated toxoid affects the antitoxin producing cells of the body in such a manner that following a second injection there is a rather prompt increase in the antitoxin content of the blood. A certain period of time must elapse between these two injections before this release of antitoxin into the blood stream takes place. It may be as short as six weeks, and as long as five years and perhaps longer. The effect of the first dose of alum toxoid is rather unique in that it cannot be replaced by the natural occurrence of tetanus and recovery from it. We have had occasion to confirm Cowles' [21] finding that a patient who had recovered from tetanus 10 years before still required two doses of alum toxoid before any demonstrable antitoxin appeared in the blood. Following the second dose, a few

days elapse before a protective titer develops. Hence, if an injury occurs during the interval between the two injections of alum toxoid and for a week or two following the second injection, passive immunization may be necessary in order to get full protection against tetanus.

The variability in the antitoxin response of different individuals following the primary series of injections, irrespective of antigen used, makes it necessary to administer a " repeat " or stimulating dose of toxoid whenever an injury occurs. Although the series of cases given a " repeat " dose of plain toxoid is small, there is a possibility suggested by our results that this plain antigen may be able to bring up the antitoxic content of the blood to the 0.1 unit level more quickly than is the case with the alum precipitated toxoid. This may be due to differences in absorption and deserves further study.

The " repeat " or stimulating dose of plain or alum precipitated toxoid produces within one week a remarkable increase in the antitoxin content of the blood. In most cases about five days elapse after the injection of the " repeat " dose before the antitoxin titer is brought up to or above the protective level. It is stated that the period of incubation of tetanus in man is usually from six to 14 days and is directly proportional to the amount of toxin and the severity of the disease. With a short period of incubation, six days or less, the disease is almost invariably fatal. Whether the mobilization of antitoxin that occurs after the injection of the " repeat " dose is fast enough to prevent all cases of acute tetanus is not definitely known, but more than likely it will be able to do so, since our minimum protective value of 0.1 unit is a conservative one. In this regard we must remember that we are dealing here with an active type of immunity that increases rapidly during the first four weeks after the " repeat " dose, when it reaches its highest level.

Between the first and third month after the " repeat " injection there is a sharp drop in antitoxin titer. Thereafter the loss is more gradual. Notwithstanding this, all subjects had a good protective titer when tested 16 months after the " repeat " dose. This is in marked contrast to the rapid antitoxin loss which these same subjects experienced after the primary course of injections, and would indicate that there is a greater permanency in the protective titer that develops after injection of the stimulating dose. This finding is in agreement with similar observations made by Jones and Moss.[31]

From our studies to date, it would appear that active immunization against tetanus by means of the injection of two doses of alum precipitated toxoid followed by a " repeat " injection upon the occurrence of an injury, will prove to be of value in military practice, in civil life where frequent injuries make the repeated injection of tetanus antitoxin impossible, and in the handling of allergic individuals who are sensitive to horse serum.

Conclusions

1. Two injections of tetanus alum precipitated toxoid produce a higher antitoxin titer than three injections of plain toxoid, when given in accordance with the schedule used in this study.

2. Following the basic course of immunization there is a rapid and variable loss of antitoxic immunity. This necessitates the injection of a "repeat" or stimulating dose of toxoid at the time of injury.

3. The "repeat" dose will bring up the antitoxin level of the blood of a previously immunized subject to a protective level of 0.1 unit or more within four to six days.

4. One week after the "repeat" dose, the antitoxin titer of an immunized subject is from two to 50 times greater than the titer produced by the injection of 1,500 units of tetanus antitoxin.

5. Following the "repeat" injection of toxoid, the protective titer seems to be maintained for a longer period of time than is the case after the basic course of immunization.

References

1. Descombey, P.: Tetanus anatoxin, Compt.-rend. Soc. de biol., 1924, xci, 239.
2. Ramon, G., and Zoeller, C.: Tetanus anatoxin and active immunization of humans against tetanus, Ann. Inst. Pasteur, 1927, xli, 805.
3. Ramon, G., and Zoeller, C.: New results concerning human vaccination against tetanus, Compt.-rend. Soc. de biol., 1929, c, 92.
4. Ramon, G., and Zoeller, C.: On the value and duration of immunity conferred on humans by vaccination with tetanus antitoxin, Compt.-rend. Soc. de biol., 1933, cxii, 347.
5. Sacquepeé, E.: Immunization against tetanus, Paris méd., 1933, i, 491.
6. Lincoln, E. M., and Greenwald, C. K.: Active immunization of human beings with tetanus toxoid, Proc. Soc. Exper. Biol. and Med., 1933, xxx, 1241.
7. Sneath, P. A. T.: Development of tetanus antitoxin following administration of tetanus toxoid, Jr. Am. Med. Assoc., 1934, cii, 1288.
8. Bergey, D. H.: Active immunization against tetanus infection with tetanus toxoid, Jr. Infect. Dis., 1934, lv, 72.
9. Bergey, D. H., and Etris, S.: Immunization of humans with alum precipitated tetanus toxoid, Am. Jr. Pub. Health, 1934, xxiv, 582.
10. Sneath, P. A. T., and Kerslake, E. G.: Further observations following administration of tetanus toxoid, Canad. Med. Assoc. Jr., 1935, xxxii, 132.
11. Sneath, P. A. T., and Kerslake, E. G.: Persistence of tetanus antitoxin in man following active immunization, Brit. Med. Jr., 1935, ii, 290.
12. Ramon, G.: The diphtheria, tetanus and staphylococcus anatoxins, and their application, Ext. de L'Echo méd. du nord, Número Spécial du May 31, 1936.
13. Ramon, G.: Tetanus anatoxin and the prevention of tetanus in man and domestic animals, Cong. Internat. de Microbiol. Londres, 1936.
14. Jones, F. G., and Moss, J. M.: Studies on tetanus toxoid. Antitoxic titer of human subjects following immunization with tetanus toxoid and tetanus alum precipitated toxoid, Jr. Immunol., 1936, xxx, 115.
15. Bergey, D. H., and Etris, S.: Active immunization against tetanus infection with refined tetanus toxoid, Jr. Immunol., 1936, xxxi, 363.
16. Bergey, D. H., and Etris, S.: Tetanus toxoid, Clin. Med. and Surg., 1936, xliii, 30.

17. Gold, H.: Studies on tetanus toxoid. I. Active immunization of allergic individuals with tetanus toxoid, alum precipitated, refined, Jr. Allergy, 1937, viii, 230.
18. Gold, H.: Studies on tetanus toxoid. II. Active immunization of normal persons with tetanus toxoid, alum precipitated refined, Jr. Am. Med. Assoc., 1937, cix, 486.
19. Hall, W. W.: Active immunization against tetanus with tetanus toxoid, Mil. Surgeon, 1937, lxxx, 104.
20. McBryde, A.: Tetanus immunization with alum precipitated toxoid, South. Med. Jr., 1937, xxx, 565.
21. Cowles, P. B.: Tetanus immunization, Yale Jr. Biol. and Med., 1937, ix, 409.
22. Jones, F. G., and Moss, J. M.: Studies on tetanus toxoid. II. The response of human subjects to an injection of tetanus toxoid or tetanus alum precipitated toxoid one year after immunization, Jr. Immunol., 1937, xxxiii, 183.
23. Jones, F. G., and Moss, J. M.: The antitoxic titers of human subjects following immunization with combined diphtheria and tetanus toxoids, alum precipitated, Jr. Immunol., 1937, xxxiii, 173.
24. Ramon, G.: Tetanus toxoid and its use and value in immunization, Ann. de méd., 1937, xlii, 358.
25. Ramon, G.: Tetanus immunity and influence of injections of stimulating adjuvant substances mixed with antigen, Rev. d'Immunol., 1937, iii, 193.
26. Gold, H.: Active immunization of allergic individuals against tetanus by means of tetanus toxoid, alum precipitated, refined, Jr. Allergy, 1938, ix, 545.
27. Gold, H.: Active immunization against tetanus by means of tetanus toxoid, alum precipitated, refined, Jr. Lab. and Clin. Med., 1938, xxiii, 903.
28. Hayden, R., and Hall, W. W.: Active immunization against tetanus using alum precipitated toxoid, U. S. Nav. Med. Bull., 1938, xxxvi, 524.
29. Boyd, J. S. K.: Active immunization against tetanus, Jr. Roy. Army Med. Corps, 1938, lxx, 289.
30. Sacquepeé, E., Pilod, M., and Jude, A.: Antidiphtheric and antitetanic immunity in adults after associated triple revaccination against typho-paratyphoid fever, diphtheria and tetanus, Rev. d'Immunol., 1938, iv, 389.
31. Jones, F. G., and Moss, J. M.: Combined diphtheria toxoid and tetanus toxoid, alum precipitated, Jr. Lab. and Clin. Med., 1939, xxiv, 512.
32. Gold, H.: On the value of a "repeat" injection of tetanus toxoid (secondary stimulus) in active immunization against tetanus, Jr. Lab. and Clin. Med. (to be published).

THE EFFECT OF ROENTGEN-RAY ON THE BLOOD CODEHYDROGENASES I AND II *

WILLIAM B. BEAN, M.D., RICHARD W. VILTER, M.D., and TOM D. SPIES, M.D., *Cincinnati, Ohio*

IT is a well known fact that therapeutic doses of roentgen-ray frequently give rise to a train of symptoms characterized by nausea, vomiting, abdominal cramps, headache and general malaise. The name "roentgen sickness" has been applied to this syndrome. Many remedies for this condition have been used with varying but often favorable results. One of the first used was parenteral liver extract.[1] More recently, thiamin hydrochloride, ascorbic acid and nicotinic acid, all of which affect cellular oxidation and reduction, have proved efficacious in the therapy of many cases.[2, 3, 4] Because of these associations, the authors thought that a disturbance of the cellular respiratory processes by roentgen-ray might explain the pathogenesis of roentgen sickness. The codehydrogenases I and II (co-enzymes), which contain the amide of nicotinic acid, appear to be catalysts of universal importance in the biological oxidations of the cell. We have therefore investigated the quantitative variation in these blood co-enzymes in patients both before and after exposure to roentgen-ray therapy.

MATERIAL AND METHOD

Eight patients were selected for study, and observations were made during a series of from one to four roentgen-ray exposures in each case. Three individuals recuperating in the hospital following herniorrhaphy and two patients with myelogenous leukemia received roentgen-ray over the spleen. Two of these cases were given 500 milligrams of nicotinic acid just before irradiation. Two pellagrins in remission, one of whom was maintained on 500 milligrams of nicotinic acid per day, were hospitalized and received roentgen-ray over the spleen. Another pellagrin in remission remained ambulatory and received roentgen-ray over the ear for the control of a basal cell carcinoma.

Repeated determinations of the blood codehydrogenases I and II were made on samples of venous blood according to the method described previously.[5, 6] Roentgen-ray was administered in courses of 200 r units (distance of 15″, milli amps 5, filters 1 mm. copper and 1 mm. aluminum, time of exposure 33 minutes),† and the amount of codehydrogenases I and II

* Received for publication July 25, 1939.
From the Department of Internal Medicine, University of Cincinnati College of Medicine, and the Cincinnati General Hospital, Cincinnati, Ohio; and the Hillman Hospital, Birmingham, Alabama. These studies were aided by grants from the John and Mary R. Markle Foundation.

† Two of the patients were treated at the Cincinnati General Hospital, and received roentgen-ray in courses of 200 r units (200 kilovolts, 15 milli amps, distance of 50 centimeters T. S. D., filter 1 thoreus, time of exposure 13½ minutes).

present in the blood was determined at intervals of 6, 12, 18, 24, 48, and 72 hours following radiation. Five hundred determinations on the blood of normal persons and patients with organic diseases served as controls.

Previous studies have shown that following roentgen-ray therapy, ether-soluble pigments which have the color of porphyrin in 25 per cent hydrochloric acid, and which are similar to those found in the urine of pellagrins in relapse, are excreted in the urine.[4] The urine of each person who received roentgen-ray, therefore, was tested for these substances before and after radiation.

Results

The representative graph, figure 1, illustrates the typical findings in one of the eight cases studied. In those cases which received no nicotinic acid the concentration of the codehydrogenases I and II in the blood de-

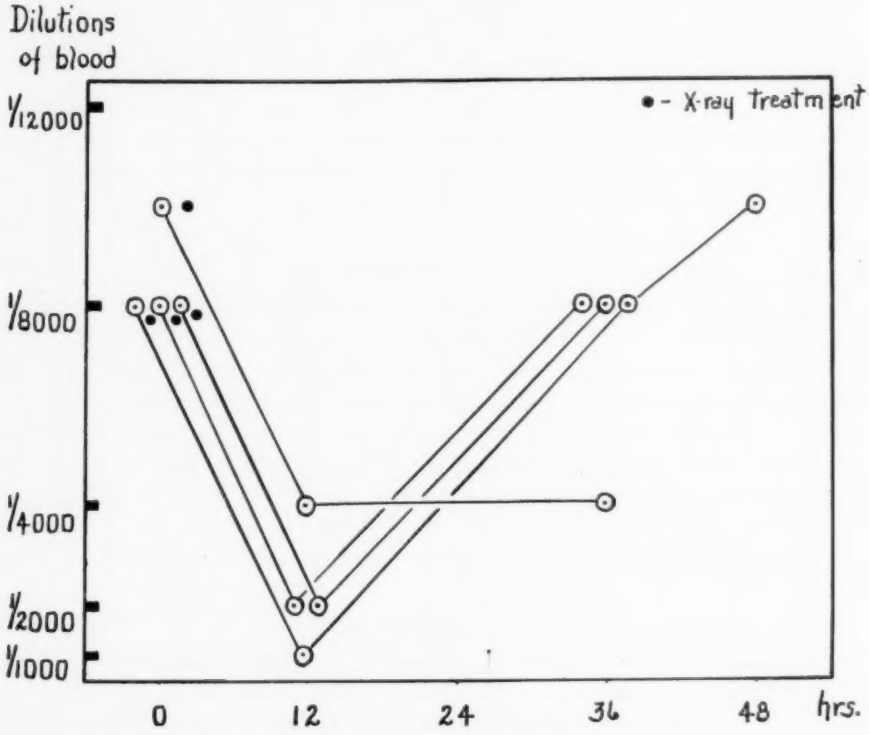


Fig. 1. Four studies of the effect of roentgen-ray treatment on the co-enzymes I and II in the blood of a pellagrin in remission as shown by the growth of *B. influenzae*.

creased 60 to 90 per cent within six to 12 hours after radiation, and then gradually increased so that after 24 hours the initial concentration was reached. On the second, third, and fourth days following roentgen-ray, the concentration of these co-enzymes remained constant. In contrast, none of

the controls showed such extraordinary and sudden decreases in the co-enzyme concentration as were observed in the persons who received roentgen-ray radiation. The pellagrin in remission who received 500 milligrams of nicotinic acid daily for two weeks did not develop roentgen sickness during a course of three roentgen-ray exposures, but after each exposure the co-enzyme concentration in the blood decreased slowly to 50 per cent of the original values. In the two persons to whom a single dose of 500 milligrams of nicotinic acid was administered just before radiation, the co-enzyme concentration decreased, but in neither case was the patient nauseated nor was there an increase in the excretion of pigments in the urine.* In all other cases, however, these pigments appeared in the urine 12 hours after radiation and disappeared within 48 hours.

Summary and Conclusions

1. Determinations of codehydrogenases I and II were made before and after roentgen-ray radiation on the blood of three healthy persons, two cases of myelogenous leukemia, and three pellagrins in remission.

2. Ether-soluble pigments which have the color of porphyrin in 25 per cent hydrochloric acid, similar in appearance to those found in the urine of pellagrins, appeared in the urine of these patients 12 hours after radiation and disappeared within 48 hours.

3. Nicotinic acid, administered before radiation, prevented the excretion of abnormal pigments but did not prevent the decrease in the co-enzyme content of the blood.

4. In those cases which received no nicotinic acid, the blood codehydrogenases I and II concentrations invariably decreased 60 to 90 per cent within 12 hours following exposure to roentgen-ray, and gradually returned to their former level at the end of 24 hours.

5. The results of this study, and the frequently reported beneficial effect of nicotinic acid and other vitamins in the treatment of " roentgen sickness " suggest that a number of cellular oxidation-reduction enzyme systems may be affected by exposure to roentgen-ray.

BIBLIOGRAPHY

1. Young, B. K.: Liver extract as a remedy for roentgen sickness, Am. Jr. Roentgenol., 1936, xxxv, 681.
2. Martin, C. L., and Moursund, W. H., Jr.: Irradiation sickness, Radiology, 1938, xxx, 277.
3. Carrie, C.: Value of vitamin C for prevention of leukopenia due to irradiation, Klin. Wchnschr., 1938, xvii, 163.
4. Spies, T. D., and Bean, W. B.: The rôle of nicotinic acid in the prevention of pellagra, roentgen sickness and increased porphyrinuria, Jr. Clin. Invest., 1938, xvii, 504 (abstract).

* The effects of yeast and wheat germ are being studied in a similar manner.

5. VILTER, R. W., VILTER, S. P., and SPIES, T. D.: Relationship between nicotinic acid and a codehydrogenase (cozymase) in blood of pellagrins and normal persons, Jr. Am. Med. Assoc., 1939, cxii, 420.
6. VILTER, R. W., VILTER, S. P., and SPIES, T. D.: Determination of the codehydrogenases I and II (cozymase) in the blood of diabetics in severe acidosis, Am. Jr. Med. Sci., 1939, cxcvii, 322.
7. VILTER, R. W., VILTER, S. P., and SPIES, T. D.: A note on the blood codehydrogenases I and II in lymphatic or myelogenous leukemia, South. Med. Jr., 1939, xxxii, 619.

THE USE OF DILATIN IN THE TREATMENT OF EPILEPSY *

By O. P. KIMBALL, M.D., F.A.C.P., *Cleveland, Ohio,* and T. N. HORAN, M.D., F.A.C.P., *Detroit, Michigan*

THE drug diphenyl-hydantoin has been known for several years but it was so nearly insoluble that it was considered practically useless. In 1937 the sodium salt of this compound was prepared in the Parke-Davis Laboratories and this drug (sodium-diphenyl-hydantoinate) was studied for anticonvulsant properties by Merritt and Putnum of Boston.[1] Because of its promise as an anticonvulsant, thorough pharmacological studies were made. Animal experimentation showed it to be practically non-toxic and to have little or no hypnotic effect. The method of excretion and end products could not be determined. From observation it was believed that there was no tendency toward storage and that it was entirely eliminated from the body within 48 hours, but in what form and by what route was unknown.

After a year's clinical use and careful animal studies, the drug was offered to us for clinical use in the Epilepsy Clinic in Detroit. During January 1938, 50 children were started on this treatment, all of whom had been under observation for months and, in many instances, for two and three years. A period of observation free from other drugs was made in all cases except those having frequent hard seizures where such procedure would obviously have been a hardship, if not a real danger.

In this paper only our clinical experience with Dilantin (sodium-diphenyl-hydantoinate) over the past 15 months will be given. A general discussion of epilepsy is not intended.

The effectiveness of Dilantin in the control of seizures has been greater than we expected. This series of cases includes 220 children and young adults, most of whom have taken Dilantin for six months or longer. Fifty have taken this drug continuously for over a year. With few exceptions, the age level is from six to 20 years, the greater number of cases being in the second decade.

In a clinical study of epilepsy the very nature of the disease precludes a satisfactory statistical report because of the many variables. The type of seizure varies from the most fleeting *petitmal* to a *status epilepticus;* the frequency may be one seizure a year in one case and in the next case, six seizures a day; the etiological factors may vary from a severe brain injury to a truly idiopathic type. Again there is the special variation associated or confused with chorea; or the more subtle variety sometimes called " epileptic equivalents " with moments of excitement and temper: Foster Kennedy's " endogenous emotional tempests."

* Received for publication May 11, 1939.

Apart from the influence on convulsions, there are other benefits from the use of Dilantin. There is a marked change in mental state and personality. This change is more noticeable if strong sedatives have been previously used. There is a definite improvement in memory and concentration. A sense of composure and sureness, with a return of social interest is evidenced within a few weeks. All of these benefits are real but hard to tabulate. In a broad way the results from the use of Dilantin may be summarized as follows:

In 55 per cent of the cases the seizures are entirely controlled.
In another 20 per cent the seizures are modified or partially controlled.
In 25 per cent there is little or no improvement.

The untoward effects can be listed as: (1) acute toxic conditions such as a skin rash or manifestations of toxic damage of the nervous system; (2) conditions suggestive of chronic irritation, coming on after two or three months' continuous use of Dilantin and gradually increasing with the continued use of the drug. Here are included sore mouth with an unusual hyperplasia of the gums, and frequently associated with these changes are repeated attacks of gastrointestinal irritability.

More specifically, in approximately 10 per cent of the cases a skin rash appears during the second week. This rash closely resembles measles, and there may be an increase in temperature to 101 degrees, and bronchial irritation. Usually, after omitting the drug for two days, treatment can be resumed. Symptoms of central nervous system intoxication are dizziness, confusion, an unsteady swaying gait, weakness, ataxia, and, in a few instances, a mild psychosis.

The most serious complications have been the unusual gum-changes and the repeated attacks of gastric irritation. The gastric upset has been seen only in cases showing the hyperplasia of the gums. They appear to be interrelated and in some way concerned with a deficiency of vitamin C. The gingival hyperplasia was first observed in June 1938, but the etiology was not known. By August, several such cases with the same history had been seen. All were on Dilantin and had complained of sore mouth two to four weeks after starting this treatment. The soreness had disappeared in about two weeks but was followed by a swelling of the gums. Fifty-one per cent of all our cases, who have been on Dilantin three months or more, show these gum changes to some extent. Our observations of these gum changes up to December 1, 1938, were recently published in the *Journal of the American Medical Association*.[2]

One important observation has been made since that paper was written, that is, that these markedly hyperplastic gums return gradually and entirely to normal within three months when the drug is discontinued, although the diet remains the same and no additional vitamin C is supplied. One girl, aged 14, had a severe hyperplasia of the gums with bleeding and soreness

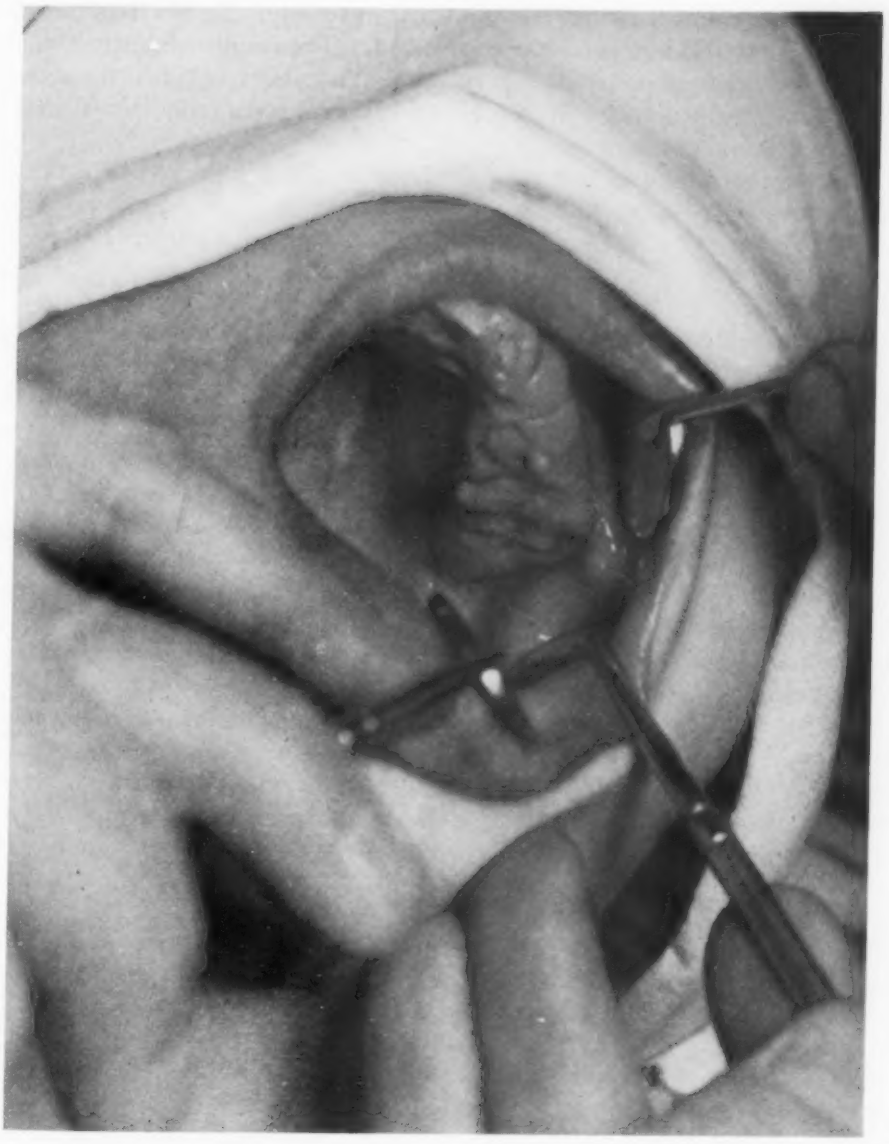


FIG. 1. This photograph of the mouth of a 10-year old girl shows only the points of the teeth above the hyperplastic gum. This photograph was taken February 21, and by March 23 the teeth were entirely covered over.

last fall. She was one of those designated as a three plus hyperplasia in the study which was reported recently. At that time her blood serum ascorbic acid was 0.12 mg. per 100 c.c. of blood. At the request of her mother Dilantin was discontinued December 1. She had no cevitamic acid and her diet was of only average or below average concentration of vitamin C. By

March 23 her gums were perfectly normal again and the blood serum ascorbic acid was 0.85 mg. per 100 c.c. of blood. The results of further study of the blood serum ascorbic acid parallel the findings reported in the recent article, namely: the decrease in ascorbic acid appears to be proportional to the severity of the hyperplasia.

On two separate cases biopsy of the hypertrophied gums has been made. Each shows microscopically a marked proliferation of the mucous membrane and connective tissue. It has the appearance of a chronic irritation and not of an infection.

Soon after our school clinic opened last autumn, we began to see attacks of acute gastric irritation, all of which were similar in history and symptoms. These cases suffered considerable pain and soreness in the epigastrium, severe nausea and vomiting and complete anorexia. Each case lasted about 48 hours. It was observed that all had been on Dilantin two months or more, and all had hyperplasia of the gums. It was found that such attacks of acute gastrointestinal upset had been occurring since April and May. Unfortunately, most of these first attacks occurred at home. Several were referred to the hospital and in two instances a diagnosis of acute appendicitis was made, immediate operation advised and performed, and in each case there were subsequent similar attacks. The temperature is always normal or below and there is no rigidity of abdominal muscles nor increase of leukocytes.

During this period a detailed study was made in one case: a young man, 19 years of age, residing in Cleveland, where circumstances permitted hospitalization whenever needed. This is the same case reported in our recent article. The relation of the gum changes, the gastrointestinal symptoms and the blood serum ascorbic acid were carefully investigated. From August 15 to September 15, the patient had received 300 mg. cevitamic acid dissolved in lemon juice daily in addition to a diet high in vitamin C. From September 15 to October 22, the excess vitamin C (cevitamic acid) was omitted but a high vitamin C diet continued. On October 22 his blood serum ascorbic acid was 0.1 mg. per 100 c.c. of blood. From October 22 to November 22, he was again given 300 mg. of cevitamic acid daily in addition to a high vitamin C diet. On November 22, his blood serum ascorbic acid was 1.8 mg. per 100 c.c. of blood. He appeared in excellent health and was stronger and happier than he had been before. At this point all citrous fruits, as well as the excess vitamin C, were eliminated. In addition to a well balanced diet he had one glass of tomato juice daily. On December 12, he developed an attack of extreme nausea, vomiting and pain in the epigastrium which lasted three days. On December 15, he was seen and referred to the hospital. At this time, his blood serum ascorbic acid was below 0.1 mg. per 100 c.c. of blood. The gums had become spongy and purplish-red and bled easily on slight pressure. For several days previous to the attack of vomiting he complained of weakness and a loss of muscular control. On December 18, gastroscopy showed no ulcers, normal motility and essentially

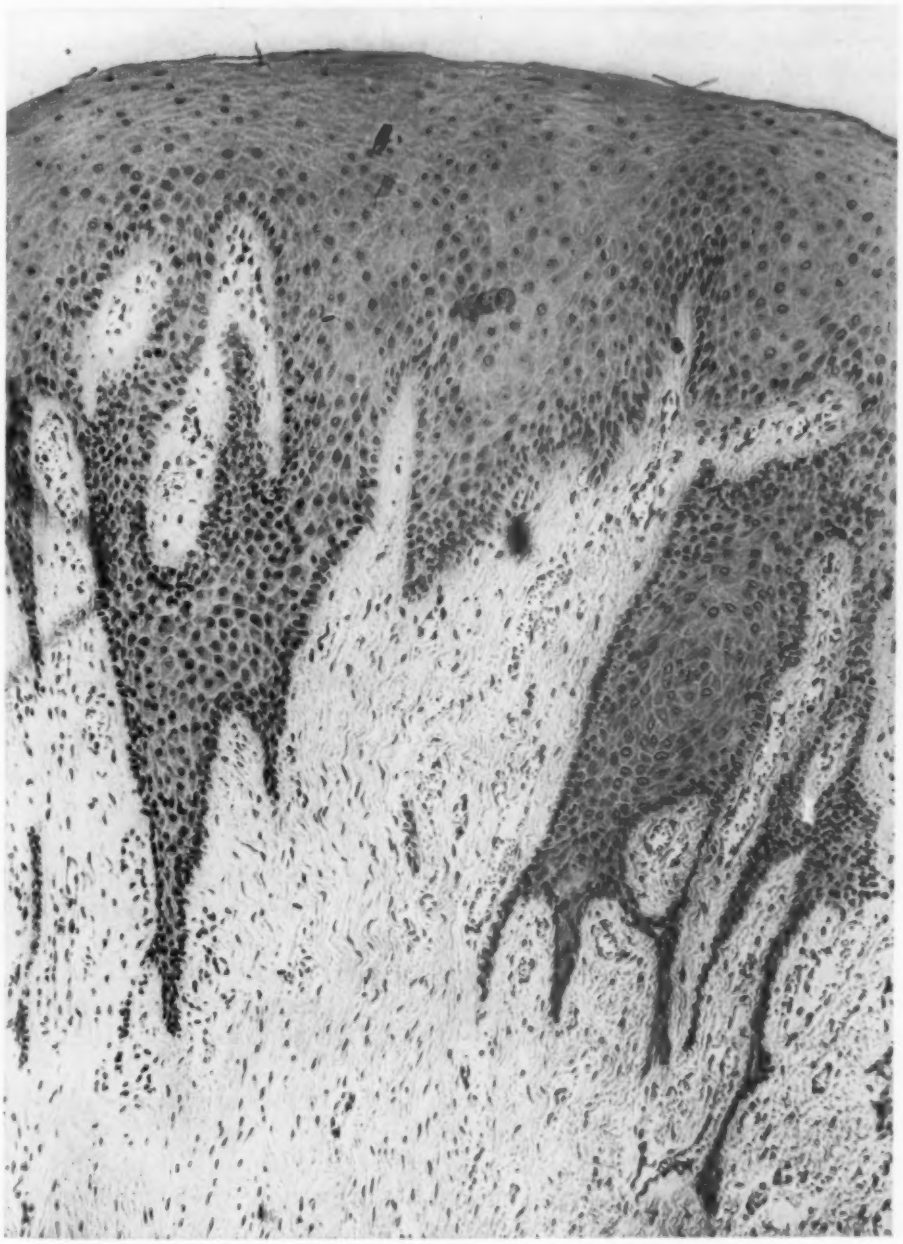


FIG. 2. Microscopic photograph of gum.

normal rugal folds of the stomach. There was a question of hypertrophy and increased redness of the rugal folds but it was not sufficiently pronounced to permit of a definite statement. On the posterior wall of the stomach there was a discolored area one inch in diameter which had been caused by a recent submucosal hemorrhage.

This gastroscopic study was made because of an unfavorable result in a similar case in Detroit. A young man above school age, who had previously been one of our students and was known to us, was taking Dilantin on our advice but under the direction of his private physician. He had taken Dilantin, 0.4 gm. daily, from July to the middle of November and his seizures had been entirely controlled. According to the history given us he suddenly developed nausea, vomiting, pain in the epigastrium, and anorexia. On the third day of his illness, although greatly improved, he had a very slight seizure because he had not been able to take Dilantin. He was up and around and was anticipating lunch, at which time he was to resume the treatment, when suddenly he started to cough and to vomit blood. This hemorrhage continued, proving fatal before the physician could arrive.

From these two cases we get a clinical picture of gastritis with hemorrhage, a condition similar to, and in some way connected with the gum changes. It appears that both of these conditions are in some way related to deficiency of vitamin C. In all, 62 attacks of gastrointestinal disturbance were observed. Since December this condition has been prevented, with few exceptions, by giving the children excess amounts of vitamin C. All are on a diet high in vitamin C and those showing gum changes are given cevitamic acid in addition to citrous fruits.

As stated above, Dilantin is the most powerful anticonvulsant thus far used. It is equally effective in the control of seizures in cases with brain injury as in the so-called "idiopathic" type. The action is so definite that in severe cases the seizures may be controlled the first day. There is no cumulative effect and the drug is eliminated within two or three days. There is no mental depression or hypnosis such as seen with heavy doses of phenobarbital and some of the commonly used patent medicines. Usually, where the seizures are entirely controlled, the amount can be reduced safely after about six months. The results have been so definite that we occasionally employ Dilantin as a diagnostic test in questionable cases of so-called "epileptic equivalents."

On Dilantin there is a definite improvement in mental faculties and emotional stability. In general, if there is no associated brain injury or mental deficiency, there is a tendency to return to normal in every way. The majority of children can receive this treatment continuously for months under careful medical supervision.

This paper was read before the Detroit Academy of Medicine, April 10, 1939, and this summary is our continued study of the same group to August 1, 1939. During April and May we saw no cases of upset and for a time thought that we had finally controlled this condition and that our experience

as related in this paper would never be repeated. However, during June and July five different cases under my observation developed attacks of severe gastric upset. One girl on two different occasions, once in June and again in July, was sent to the hospital with the diagnosis of appendicitis for operation. The absence of fever, abdominal rigidity and leukocytosis held up the operation each time. In this case the gums showed marked hyperplasia, sponginess with bleeding and soreness. No blood serum ascorbic acid determination or gastroscopic study was made. These five cases were all on a diet high in vitamin C, but none was taking extra vitamin as cevitamic acid.

We have no satisfactory explanation for this variation in number of cases of gastric irritation seen during this past year. Whether there is naturally a low intake of vitamin C during the fall and winter months, or whether we brought about an abnormally high vitamin C intake during the spring months by our insistence on such a diet can not be determined. Possibly there is some other factor.

To date we are unable to prevent all of the cases of acute gastric distress, but will continue the use of Dilantin with even more emphasis on a high vitamin C diet and with a recheck each month for symptoms suggesting the onset of these toxic phenomena.

REFERENCES

1. Merritt, H. H., and Putnum, T. J.: Sodium diphenyl-hydantoinate in the treatment of convulsive disorders, Jr. Am. Med. Assoc., 1938, cxi, 1068.
2. Kimball, O. P.: The treatment of epilepsy with sodium diphenyl-hydantoinate, Jr. Am. Med. Assoc., 1939, cxii, 1244.

SOME STUDIES IN THE MECHANISM OF CARDIAC HYPERTROPHY *

By GEORGE HERRMANN, M.D., F.A.C.P., and GEORGE M. DECHERD, JR., M.D., F.A.C.P., *Galveston, Texas*

HYPERTROPHY of the heart is a reliable sign of heart disease. A definitely enlarged heart is foredoomed to failure. The functional disadvantages of enlargement of the myocardial fibers have been stressed by Harrison, Ashman, et al.[1] and by Wearn, Roberts, et al.[2] Cardiologists have held that recognizable hypertrophy is always pathological, progressive, irreversible and eventually detrimental. The argument that heart muscle hypertrophy may be advantageous like that of skeletal muscle, as exemplified by the blacksmith's biceps, may be countered with the argument that Sandow was really muscle-bound. The bulging muscle makes a striking show, but the long sleek muscle strikes the sharper blow.

The not infrequent case of chronic hypertension without cardiac enlargement and the question of the reversible heart have intrigued us. There have been opinions voiced recently that hypertrophy may be curtailed and that it may actually be reversible. Christian [3] advocated the use of digitalis to restrain hypertrophy on the basis of Cloetta's observations.[4] Matas and Heninger [5] have recently emphasized the disappearance of hypertrophy upon closure of an A–V aneurysm. Such facts have excited the interest of clinicians, as well as pathologists, in the processes concerned in myocardial overdevelopment. The clinician wants to know what factors contribute to pathological cardiac hypertrophy and what steps might be taken to curtail or reverse the processes. This calls for consideration of clinical and experimental data.

Normal hearts do not hypertrophy in the clinical and pathological sense as a result of physical activity, exercise, training, competitive athletics and feats of strength and endurance. These must put some strain upon the heart, but in practically all studies of athletes, with the exception of those of Tung et al.[6] on ricksha-pullers, no recognizable enlargement has been found. Some compensatory chemical, physiological and histological changes must result from strenuous preparatory efforts, yet in most athletes our inadequate clinical methods fail to reveal any changes. The point at which physiological strengthening ends and pathological hypertrophy begins is difficult of establishment. Clinically a heart with its point of maximum apex impulse inside the nipple line we accept as normal, and must consider as ab-

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

From the Department of Medicine, University of Texas Medical School.

Aided by Grants Nos. 444 and 530 of the Committee on Scientific Research of the American Medical Association.

normal any detectable displacement of the point of maximum impulse of the heart's apex or extension of the borders of the heart beyond the left midclavicular line or the right sternal border. These signs indicate cardiac enlargement which, even though largely dilatation, still spells heart disease. The diagnosis of cardiac hypertrophy should be reserved and questioned until actually increased weights have been obtained, or the ventricular thickness has been demonstrated by Robb's method.[7]

Work hypertrophy apparently is compensatory and aids in the maintenance of circulatory equilibrium in progressive hypertensive arteriolar disease, chronic cardiac valvular disease, and mediastinal or parietal anchorage of an adherent pericardium. But in all of these there are, in addition to the added work, other factors such as progressive arteriolar changes, inflammatory reactions, with scar tissue or coronary artery constriction. As the demands persist, the damaged human heart overdoes matters and responds to injury and the extra burden with pathological cardiac hypertrophy. The mechanism of production of pathological cardiac enlargement as well as the adequacy and efficiency of such hearts, are still open questions. There is more than a little doubt that it is a response to the added work stimulus or dilatation alone. It is an interesting fact that by no means of experimentation thus far have we been able to produce any extreme grade of cardiac hypertrophy in animals comparable to that seen in humans.

The enlargement of the heart in *arteriovenous aneurysm* is 90 per cent to 75 per cent dilatation, and all but 10 per cent to 25 per cent will be removed by closure of the fistula. The longer the A–V communication remains open, the more genuine hypertrophy develops and the less likely is complete reversibility possible.

The cardiac enlargement occasionally found in the *myxedematous* patient is not cardiac hypertrophy in the restricted sense; pathologically, physiologically and chemically it differs from that of hypertensive disease. It is the result of a metabolic disorder of the heart muscle, as of all tissues, with an increased retention of water. It disappears under the stimulus of thyroid extract medication.

The *beri-beri* heart is likewise not a true myocardial hypertrophy but a disturbance in the cardiac cellular metabolism that weakens the myocardium and leads to increase in the size of the heart. The enlargement vanishes with the building up of the vitamin B content of the body.

The fact that the clinician accepts cardiac hypertrophy as a pathological process creates the stimulus for the studies directed toward determination of the causes and the methods for the prevention of this over-compensatory development. A consideration of the main theories that have been propounded in explanation of cardiac hypertrophy is in order in the beginning of a discussion of the subject.

Some Theories of the Mechanism of Cardiac Hypertrophy

The many theories of hypertrophy of the heart are exhaustively discussed by Mönckeberg.[8] We present a skeleton abstract of Mönckeberg's survey, with some additions from the recent literature.

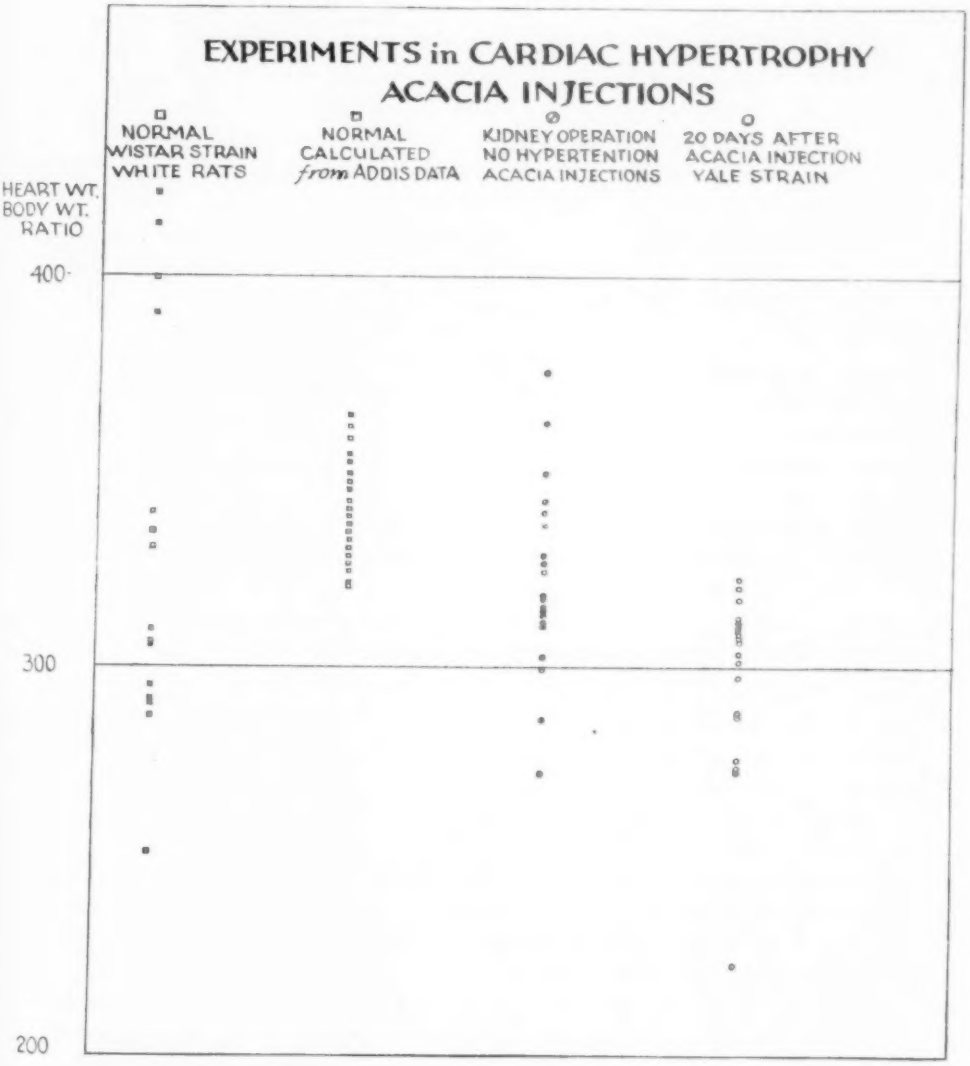
The pure work hypothesis of cardiac hypertrophy was advanced by Cohnheim who observed that the heart chamber that was called upon to bear an extra burden showed cardiac hypertrophy. Cohnheim stated that aside from extra work there was no other physiological pathological moment that could cause muscle to develop beyond its normal growth level. He insisted that when there was an increase in the number or thickness of the myocardial cells or fibers one could conclude absolutely that the muscle had been called upon to do more than its normal amount of work over a long period of time. Thorel maintained that in spite of muscular exertion the normal heart does not develop hypertrophy. Most of the older pathologists agreed that the normal heart would increase somewhat in size under the stimulus of exercise. However, it was not clearly established when strengthening of the normal heart stopped and work hypertrophy as a pathological process began.

Rothberger taught that the heart might enlarge from other causes, perhaps as a result of increased supply of nourishment. Rosenbach pointed out that increased nourishment was merely part and parcel of the reaction to effort, with increased coronary flow merely a response to the demand. Koester suggested that the increased length of the diastasis period was all-important, inasmuch as there was a compression of the coronary vascular bed during systole, with resulting ischemia of the heart muscle. In complete diastole, too, there is such stretching of the coronary vascular bed that the intramural circulation is embarrassed during this phase. Hence the importance of diastasis, the period between the two extreme phases when the greatest flushing of the coronary blood, with its nutritional material, takes place. Prolongation of the period of diastasis may therefore lead to greater assimilation and hypertrophy.

Letulle, Rindfleisch and Orth came to the conclusion, upon the basis of histological studies, that in hypertrophy there was multiplication of the cells or splitting of fibers. Tangl, Forster and Zielonko, however, maintained that in cardiac hypertrophy there was enlargement of the individual cells but no increase in number. Tangl furthermore could demonstrate no increase in the number of nuclei and concluded that hypertrophy consisted in increase in size and volume of the individual heart muscle cells. Romberg and Hasenfeld verified these contentions in the rabbit's heart after experimental aortic incompetency. Belints produced with experimental aortic regurgitation in dogs, cats and rabbits, work hypertrophy of the heart that seemed to be closely correlated with the grade of the burden imposed. Stadler found that hypertrophy was not limited to the chamber that bore the brunt of the overload.

Albrecht conceived of physiological as well as morphological properties

of hypertrophied muscle which would insure greater functional capacity. In certain hypertensive chronic nephritics, for instance, he pointed out that the right ventricle, as well as the left, undergoes some hypertrophy, while in other nephritics there is no hypertrophy at all. Albrecht further noted in his own studies and those of others a definite concomitant increase in the inter-



stitial and parenchymatous changes as pathological processes in which hypertrophy may be considered to be only a secondary manifestation. Albrecht felt that toxins and pathologically impaired local myocardial nutrition in chronic nephritics caused interstitial myocardial disease and acted as the stimulus to hypertrophy. A connective tissue increase in the hypertrophied

heart has been commented on by others. In this connection it is interesting that in recent studies, Bartels and Smith found cardiac hypertrophy in 26 out of 42 cases with myocardial infarction. Davis and Blumgart reported six greatly hypertrophied hearts out of 31 hearts with advanced coronary sclerosis, and 16 hypertrophied out of 17 with comparable arteriosclerotic disease but with added congestive failure. The congestive failure they therefore thought contributed to the hypertrophy.

Tangl sharply opposed the idea that the interstitial processes had anything to do with hypertrophy, on the basis of the absence of such changes in the early stages of hypertrophy in experimental work. Dehio carefully restudied the whole problem and attributed the myofibrosis to the stasis in the myocardial capillaries incident to the increased diastolic pressure in the dilated ventricle. This he stated is the stimulus to fibroblastic proliferation. There is much argument pro and con in the German literature concerning the significance of these interstitial findings. Albrecht has emphasized the fact that mechanical and chemical toxic stimuli may result in hypertrophy. Horvath revived the law of Fick for skeletal muscle, in which increased initial load and stretching were related to the work, and applied it to the heart. He referred to the stretching of the muscle as the stimulus to hypertrophy.

Starling [9] propounded the law of the heart which stated the important relation between the initial load represented by the venous pressure, the diastolic volume or the initial length of the ventricular muscle scroll, and the volume output of blood from the heart chambers. He found that coordination between the diastolic volume and systolic output of the heart represented by the venous pressure determines the initial length of the ventricular muscle fibers. Abnormal strains increase the initial load and to such may be attributed dilatation or stretching. This is a common precedent to hypertrophy. The significance of the dilatation in both phases of systole and diastole is an increase in the demand on the myocardium and its blood supply. Under such conditions ventricular contraction or systole is accompanied by an incomplete emptying and dilatation in the diastole and by an overfilling of the cavity. The increased pressure must be resisted by the ventricular wall, and a vicious circle is thus created. The dilatation contributes the overstretching stimulus to maximal contraction and hypertrophy. An occasional hypertensive patient's heart which has not been dilated may be the seat of concentric hypertrophy and show relatively little functional incompetency and histologically no fibrosis.

Stewart [10] explained his experimental finding of general hypertrophy involving the right ventricles and the auricles as well as the left ventricles in dogs with aortic regurgitation, on the basis of an intracardiac reflex which coördinated the work of all chambers. Stewart held that parenchymatous damage leads to enlargement of heart muscle cells, and interstitial changes and stretching to myofibrosis. Herrmann [11a] corroborated Stewart's observations of multichamber involvement and added the observation that in the presence of secondary infectious valvulitis considerably greater degrees of

EXPERIMENTAL STUDIES in CARDIAC HYPERTROPHY
HEART WEIGHT - BODY WEIGHT RATIOS AFTER ACACIA INJECTIONS
POST INJECTION INTERVALS IN DAYS
HEART WEIGHT
BODY WEIGHT
RATIO
4.00
3.00
2.00
1.00
DAYS 0 2 4 6 8 10 20 30 40 50 60 75 100 200 300
IMMEDIATE DEATH - PULMONARY EDEMA
NERVE OPERATION ‡ HYPERTENSION
KIDNEY OPERATION ‡ HYPERTENSION
ACACIA INJECTIONS single
" " multiple
" " single digitalized
" " multiple digitalized

cardiac hypertrophy resulted than were found in dogs with uninfected aortic regurgitation. In this large series of 70 dogs with experimental aortic regurgitation the age of the animals at the time at which the lesion was produced seemed to be another factor besides infection in determining the grade of hypertrophy. The postoperative interval was likewise of some importance and, although Stewart had reported hypertrophy within 10 days, the earliest evidence in this series was found after 19 days. In studies with Mims Gage [11b] the hearts of dogs with experimental arteriovenous aneurysm were shown by heart weight/body weight ratios to be slightly but definitely hypertrophied. In one dog that lived seven years a 100 per cent hypertrophy was produced.

In studies with E. H. Schwab [11c] in rabbits with experimental aortic insufficiency the location of the damaged cusp seemed to be significant.

Hartmann [12] presented data to the effect that cardiac hypertrophy followed the production by roentgen-radiation of nephritis in dogs. Besides teleoroentgenographic and electrocardiographic evidence he found heart weight/body weight ratios up to 0.11 instead of the normal 0.07. There was, however, no definite correlation between the hypertension which was produced in the majority of animals and the degree of hypertrophy. The latter was greater than might be expected from the blood pressure. The hypertrophy seemed to have developed by the time that the hypertension became definite.

Eyster, Meek and Hodges [13a] demonstrated by frontal plane teleoroentgenograms an increase in heart volume appearing immediately after aortic regurgitation was experimentally produced in dogs. They found that this enlargement disappeared after a few days and the heart returned to its normal volume or even to subnormal size. Following this there was a gradual hypertrophy which reached a maximum after about 70 to 100 days. A second lesion superimposed on the first caused a second period of transitory dilatation and was followed by a subsequent period of additional hypertrophy. Bazett [14] questioned the occurrence of the early dilatation as a result of stretching which he was unable to demonstrate. He attributed the apparent enlargement to changes in rate. Holman [14b] showed that bleeding an animal followed by subsequent infusion of the same blood gave similar changes in the teleoroentgenograms.

Eyster [13b, c] reported macroscopic and microscopic evidence of stretching and injury of the heart muscle during this short period of primary dilatation, and concluded that the stimulus to hypertrophy was the overstretching of the myocardial scrolls to the point of injuring them. Eyster further reported that a constricting rubber band placed around the aorta for three to six days and then removed caused the hearts to hypertrophy progressively thereafter. To test out this hypothesis further Eyster produced temporary cardiac overload, with stretching of the heart muscle beyond its physiologic limits and consequent muscle injury in a series of 11 dogs, by massive transfusions of 75 per cent to 100 per cent of their blood volume. He demonstrated the same changes in the teleoroentgenograms as had followed experimental aortic

regurgitation. On two of these dogs he showed heart size increases of 13.5 per cent lasting five days, decreasing to + 3.5 per cent, rising to + 18 per cent in 122 days, rising to + 22 per cent after the second transfusion, falling to + 10 per cent in seven days, and increasing to + 25.5 per cent on the one hundred sixty-eighth day. So far as we can find out Eyster has not published any heart weights or ratios on the transfused dogs. The experiments should be repeated and the postmortem ratios determined. Eyster stated that a prolonged period of increased work was not necessary to produce hypertrophy, since a single insult, such as a transitory overstretching, would cause hypertrophy.

If the single initial injury hypothesis could be supplemented by the support of actually demonstrated increases in the weights of hearts subjected to temporary dilatation, there would be established a fundamental basis for the explanation of all types of cardiac hypertrophy known to occur in various clinical conditions. In most of these we can assume not only dilatation as a sequel to increased load, but in addition myocardial anoxemia and toxic or inflammatory myocarditis as further factors in initiating hypertrophy. A continuance of the extra burden or a part of it is much more common than a total subsidence of the same. Any pathologic lesion in the myocardium would interfere with the efficiency of the heart action and add to the burden. Hypertrophy in response to inefficient function would then be a manifestation of myocardial weakness.

It is not necessary to comment upon the frequent association of cardiac hypertrophy with valvular lesions and with increased arterial resistance, other than to emphasize the not uncommon absence of any evidences of hypertrophy in the hearts of some patients known to have had hypertension for years antemortem. In contrast to this are the observations of Willius and Smith [17] of hearts with hypertrophy far out of proportion to the valvular lesions in acute rheumatic carditis of known short duration. Similarly marked increase in heart weight is a typical finding in the so-called Fiedler's myocarditis,[18] where valve lesions are absent. Inflammatory edema and infiltration make up a large part of the increase in weight in the acute myocarditis cases and may interfere with efficient function.

Lewis and Drury [15] attributed the cardiac enlargement in arteriovenous fistulae to *impaired coronary filling,* though this does not adequately explain the preponderant enlargement of the right side of the heart, nor does it, as Porter and Baker [16] point out, seem reasonable as the sole explanation of a phenomenon that will largely disappear within a few weeks after closure of the fistula. The cause in our opinion, is a combination of dilatation and decreased coronary blood flow.

Smith and Bartel's [19] group of cases with hearts from 9 per cent to 108 per cent larger than normal (averaging 44 per cent) with no factor predisposing to this other than *occlusion* of one or more of the *coronary* vessels is difficult to explain. The possibility of a previous hypertensive state has not been absolutely ruled out. The findings have been denied by both clini-

cal and experimental investigators. In addition, occasional cases have been seen of hypertrophy in hearts whose left coronary supply had an anomalous origin from the pulmonary artery. Davis and Blumgart [20] have recently advanced strongly suggestive evidence that coronary arteriosclerosis may be the sole etiologic agent leading to myocardial hypertrophy, though unfortunately they make no note concerning the renal arterioles in their cases, and hence may have included cases of subsided essential hypertension.

Anemia, though this is uncommon clinically, may appear to be the sole factor that is associated with an hypertrophied heart, and this set of circumstances has been duplicated experimentally. Again, while the evidence is not conclusive that *lowered oxygen tensions* may lead to cardiac hypertrophy in humans, in experimental animals marked reduction of the barometric pressure, or decrease in the oxygen content of the environmental atmosphere will lead to indisputable increases in the heart weights. In short, sharp increase in the ventricular load, inflammatory changes in the myocardium, or myocardial anoxemia, all of which lead to cardiac dilatation, are conceivable factors in all types of cardiac hypertrophy.

The Present Studies

The Rabbit Series. Our experiments were designed to test out the theory of initial injury as the stimulus to progressive cardiac hypertrophy. As the initial load that would produce cardiac dilatation and strain, we used 6 per cent and 12 per cent buffered acacia solution, introduced rapidly intravenously in a volume equal to the blood volume, or $\frac{1}{14}$ of the animal's weight. Most of the series of rabbits averaged three months in age and weighed about three pounds each. They were given the acacia solution through the ear veins under pressure, over a period of five to 15 minutes. More than 100 rabbits were used, of which about 10 per cent died immediately as a result of acute pulmonary edema. This was considered conclusive evidence that there was a maximal strain put on the heart by this procedure.

After the injection of the acacia solution in the series the hemoglobin was routinely found to be about 50 per cent of what it had been previously, indicating about what dilution of the blood had been made. In general, the hemoglobin level was back to normal in four to seven days after the first injections. In a small series of animals the acacia injections were repeated at weekly intervals for two or three weeks, maintaining the hemoglobin at about 50 per cent to 75 per cent of normal. In these the hemoglobin took somewhat longer to return to normal.

After the injections the animals were divided into two groups. In the first group nothing further was done (the animals were fed and kept in small individual cages), whereas the other group received regularly, twice a week, 0.25 cat units of Digalen * or Digifolin.† The rabbits were sacrificed at

* Supplied by Hoffmann La Roche Co., Nutley, N. J.
† Supplied by Ciba Co., Summit, N. J.

varying periods of time from a few days to 300 days. The hearts were removed and carefully weighed, the body weight was taken, and HW/BW ratios were estimated. As a normal for this series we used the HW/BW ratio for rabbits of the same age from the same source, that had had carotid sinus operations without the production of hypertrophy (HW/BW 2.16), and rabbits that had had unilateral nephrectomy and the cutting down of the circulation of the other kidney without resulting hypertension (HW/BW 2.25).

The mean for the HW/BW ratios of the rabbits that had been given a single injection of acacia alone and not treated otherwise was higher (2.68) than that for any other group, but the increase was not statistically significant. There was, however, no further increase in HW/BW ratio whatsoever nor any significant difference between the animals sacrificed after 62 days (HW/BW 2.83), 240 days (HW/BW 2.58), and those sacrificed after about 300 days (HW/BW 2.71).

The rabbits that had received a single acacia injection and were subsequently digitalized showed a slightly lower mean HW/BW ratio (2.57) but again the difference was not statistically significant. Likewise the animals that were digitalized before the acacia solution was given had a still lower mean HW/BW ratio (2.37) which is also not statistically significant. The few animals that received 6 per cent acacia had slightly smaller hearts than those that were infused with 12 per cent acacia, but this was not established statistically. Multiple acacia injections with the persistent anemia produced for three weeks did not seem to act as a stimulus to hypertrophy. The multiply injected acacia animals that were digitalized had the lowest HW/BW ratio mean of the group (2.08), but there were so few of them that they were not statistically significant. The HW/BW ratios in these series were higher than those that we have gotten as our previous normal HW/BW ratio (1.98) but not higher than the normals of other investigators, nor were they higher than the normals for the present series.

The White Rat Series. White rats of the Wistar strain and of the Yale strain were injected with 12 per cent buffered acacia solution in a volume equal to $\frac{1}{14}$ the body weight, just as the rabbits had been injected. The calculated amount of solution was introduced into the rats through the femoral vein, within a period of about five minutes. Many developed pulmonary edema, but only 5 per cent died from it. Twenty of the rats were males of the Wistar strain weighing 200 to 300 gm. and had previously been operated upon and had the blood supply to the left kidney reduced by a ligature (using a wire similar to Collins', 0.4 mm. in diameter) over the artery. None of these white rats showed any hypertension subsequent to the operation, in fact the blood pressures ranged from 60 to 100 mm. of mercury. The other 20 were fresh Yale strain males weighing 175 to 225 gm. each.

Only 20 days were allowed for the hypertrophy to develop in these two

series of rats, but this seemed to be sufficient since in other studies, particularly Rytand's,[21] hypertrophy was reported to have developed after a comparable length of time following renal artery compression. The HW/BW ratio mean of the operated Wistar rats that had been injected with acacia was slightly higher (3.22) than that in the rats of the Yale strain series in which acacia alone was given (3.04). Thus the differences from normal were not significant. Both means were lower than the normal HW/BW ratio calculated from Addis' formula, which was 3.40 for rats weighing between 150 and 250 gm., while the normals in our own series that had died acutely at operation or during the experiment gave a normal HW/BW ratio of 3.37.

Comments

These experimental data from both the rabbit series and the rat series fail to corroborate, with statistically significant differences, the Horvath-Eyster hypothesis. The stretching of the heart with an overload of acacia solution to the point of producing pulmonary edema is perhaps not strain enough to exhibit initial injury of the necessary grade.

Table I

Data on Attempts to Produce Cardiac Hypertrophy in Rabbits

Experiment	No.	HW/BW Ratio Mean ± PE_{Mean}	Standard Deviation
1. Nerve operations—No hyp.	5	2.16 ± 0.12	0.42
2. Kidney operations—No hyp.	25	2.25 ± 0.06	0.46
3. Acacia-pulmonary edema	13	2.25 ± 0.08	0.42
4. Acacia injection alone	27	2.68 ± 0.07	0.53
5. Acacia and digitalis	22	2.57 ± 0.06	0.44
6. Predigitalized acacia	5	2.37 ± 0.09	0.30
7. Multiple acacia	4	2.44 ± 0.11	0.33
8. Multiple acacia and digitalis	4	2.08 ± 0.08	0.24

Table II

Heart Weight/Body Weight Ratios on White Rats 20 Days after Injection of Acacia

	HW/BW Ratio Mean ± PE_{Mean}	Standard Deviation
1. Normal (Addis) *	3.40 ± 0.06	0.43
15. Normal (ours)	3.37 ± 0.09	0.52
20. Previously operated– Acacia later	3.22 ± 0.08	0.54
20. Acacia only (Yale)	3.04 ± 0.05	0.36

* Calculation from Addis formula for rats, 150–250 gm.

The acacia solution should have been as effective as Eyster's 75 per cent to 100 per cent increases in blood volume transfusion. Eyster's conclusions, therefore, cannot be substantiated.

We were further disappointed in that the digitalized acacia rabbit series did not show statistically significant differences from the non-digitalized series. The mean HW/BW ratios were lower but not significantly so. We may thus question the validity of Cloetta's conclusions.

On the basis of our data we feel that the injury that results from temporary dilatation alone is not sufficient to produce cardiac hypertrophy.

BIBLIOGRAPHY

1. Harrison, T. R., Ashman, R., and Larson, R. M.: Congestive heart failure: relation between thickness of cardiac muscle fiber and optimum rate of heart, Arch. Int. Med., 1932, xlix, 151.
2. Wearn, J. T., Roberts, J. T., and Badal, J. J.: Capillary-muscle ratio in normal and hypertrophied human hearts, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 322.
3. Christian, H. A.: The use of digitalis other than in the treatment of cardiac decompensation, Jr. Am. Med. Assoc., 1933, c, 789.
4. Cloetta, M.: The effect of digitalis upon the normal and pathologic heart, Arch. Exper. Path. and Pharm., 1908, lix, 209.
5. Matas, R., and Heninger, B. R.: Reversible cardiac enlargement in a case of congenital cavernous hemangioma, Am. Heart Jr., 1939, xvii, 131.
6. Tung, C. L., Hsieh, C. K., Bien, C. W., and Dieuaide, F. R.: The hearts of rickshapullers, Am. Heart Jr., 1934, x, 79.
7. Robb, G. P., and Steinberg, I.: Visualization of the chambers of the heart, Am. Jr. Roentgenol. and Therap., 1939, xli, 1.
8. Mönckeberg, J. G.: Myokard und specifisches Muskelsystem bei Störungen des Klappenmechanismus und bei sonstigen zur Hypertrophie führenden Erkrankungen, Handbuch der speziellen pathologischen Anatomie und Histologie, Band II, Herz und Gefässe, 1924, ii, 349.
9. Starling, E. H., and Visscher, M. B.: The regulation of the energy output of the heart, Jr. Physiol., 1927, lxii, 16.
10. Stewart, H. A.: The mode of action of adrenalin in the production of cardiac hypertrophy, Jr. Path. and Bact., 1912–13, xvii, 64.

11*a*. Herrmann, G. R.: Experimental heart disease. II. With a consideration of some factors concerned in cardiac hypertrophy, Am. Heart Jr., 1926, i, 485.

11*b*. Gage, I. M., and Herrmann, G. R.: Cardiac hypertrophy in A–V aneurysm, Proc. Soc. Exper. Biol. and Med., 1928, xxv, 765.

11*c*. Schwab, E. H., and Herrmann, G. R.: Experimental ablation of posterior as contrasted to anterior aortic cusp on cardiac hypertrophy in rabbits, Proc. Soc. Exper. Biol. and Med., 1935, xxxiii, 410.

12. Hartmann, F. W., Bollinger, A., and Donl, H. P.: Cardiovascular response in experimental nephritis, Jr. Am. Med. Assoc., 1927, lxxxix, 1936.

13*a*. Eyster, J. A. E., Meek, W. J., and Hodges, F. J.: Cardiac changes subsequent to experimental aortic lesions, Arch. Int. Med., 1927, xxxix, 536.

13*b*. Eyster, J. A. E.: Cardiac dilatation and hypertrophy, Trans. Assoc. Am. Phys., 1927, xlii, 15.

13*c*. Eyster, J. A. E.: Experimental and clinical studies in cardiac hypertrophy, Jr. Am. Med. Assoc., 1928, xci, 1881.

14*a*. Bazett, H. C.: Further observations on experimental aortic regurgitation, Am. Jr. Physiol., 1925, lxxii, 201.

14*b*. Holman, E.: Significance of temporary elevation of blood pressure, following splenectomy with particular reference to rôle of spleen as a regulator of circulation, Surgery, 1937, i, 688.

15. Lewis, T., and Drury, A.: Observations relative to arteriovenous aneurysm, Heart, 1923, x, 301.
16. Porter, W. B., and Baker, J. B.: The significance of cardiac enlargement caused by arteriovenous fistula, Ann. Int. Med., 1937, xi, 370.
17. Willius, F. A., and Smith, H. L.: Factors concerned in cardiac hypertrophy, Am. Heart Jr., 1934–35, x, 190.
18. Scott, R. W., and Saphir, O.: Acute isolated myocarditis, Am. Heart Jr., 1929, v, 129.
19. Bartels, E. C., and Smith, H. L.: Gross cardiac hypertrophy in myocardial infarction, Am. Jr. Med. Sci., 1932, clxxxiv, 452.
20. Davis, D., and Blumgart, H. L.: Cardiac hypertrophy: its relation to coronary arteriosclerosis and congestive heart failure, Ann. Int. Med., 1937, xi, 1024.
21. Rytand, D. A.: Renal factor in arterial hypertension with coarctation of the aorta, Jr Clin. Invest., 1938, xvii, 391.

A METHOD OF TESTING CARDIAC FUNCTION*

By Dan G. Stine, M.D., F.A.C.P., *Columbia, Missouri*

The Problem

For a period of 10 years we have interested ourselves in the effect of athletic exercise upon the heart. These observations, on more than 400 athletes during their university residence, were presented to the American Student Health Association at its 1937 meeting in Chicago and were published in the Proceedings of the organization.

The result of these observations indicated definitely that the response of the heart to exercise depended not upon the exercise but upon the integrity of the heart's mechanism, and that hearts with slight departures from perfection in their mechanism were much more common among athletes than had been generally assumed. If this defect impaired the ability of the heart normally to carry out its function, the heart compensated for this by enlargement, whereas the undamaged heart of an athlete undergoing the same amount of exertion in the same sports would be normal in size.

During this period of observation, it was found that the percentage of enlarged hearts varied from year to year, the extremes being 6 per cent and 17 per cent, and the average being about 10 per cent. Each year it was found that the athletes whose cardiac measurements were above normal presented evidence of cardiac damage.

The procedure of estimating cardiac size is not a simple one. There is not a uniformity of opinion in regard to how accurately this can be done. We have sought for a method by which heart size can be accurately measured. The heart being a three-dimensional organ, its size may be expressed by volume or by weight.

Bardeen has checked the relation between heart volume, transverse diameter, and area, by anatomical measurements in the cadaver, and he found that their interrelation was sufficiently constant to justify the use of transverse diameter and area as an index of heart volume.

For practical purposes radiological measurements of the heart are limited to the transverse diameter and area of the frontal silhouette. Area involves, besides the experimental error in obtaining the heart outline, a further error in measuring it, and for this reason we prefer the transverse diameter as the index of the heart size. The volume of the heart varies directly with the cube of the transverse diameter so that quite small changes in transverse diameter correspond to considerable changes in volume. The relation of transverse diameter to volume is not a constant one for it varies with the position of the heart in the chest. This variation in the lie of the heart is

* Received for publication August 26, 1938.
From the Student Health Service of the University of Missouri.

FIG. 1. Stethoscope applied to chest at beginning of test.

FIG. 2. Test carried out at the rate of 35 squats per minute.

roughly neutralized if the transverse diameter is correlated with both body height and weight.

We have felt that the transverse diameter of the heart can be fairly accurately measured by roentgen-ray and that it is the most satisfactory and practical guide for estimating the size of the heart.

The left auricle may enlarge without affecting the transverse diameter, but we will describe later a technic for estimating its size. An increase in size of any of the three remaining chambers will result in an increase in the measurement of the transverse diameter.

M. R. Student. Track (2 mile run); aged 21; ht. 68¼ in.; wt. 161 lbs. Transverse diameter. 14.2 cm. Esophagram—no distortion. E. K. G. normal. No murmurs.

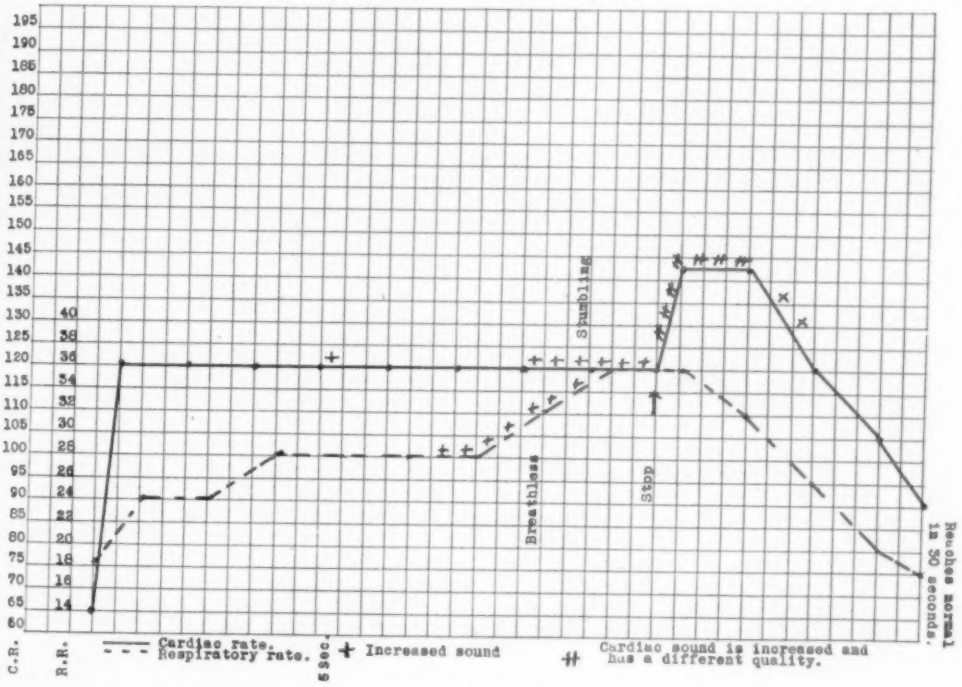


CHART 1. An excellent response to the test by a normal, well trained heart.

A definite decision as to whether or not a heart is enlarged can be made only if the transverse diameter is compared with some standard which will state what the diameter of the heart of an individual should be, if that individual's heart were normal.

In 1919, Danzer suggested the use of a ratio between the cardiac and thoracic transverse measurements as a standard. According to this standard, a heart is normal in size when its transverse diameter approximates one-half the internal diameter of the thorax, and is enlarged when the transverse diameter exceeds 50 per cent of the internal diameter of the thorax. In our

study we found no striking relationship between the intrathoracic and the cardiac transverse diameter.

In 1926, Hodges and Eyster, of the University of Wisconsin, published a most excellent work establishing the relationship of the transverse diameter of the heart to the height and weight of the body. In this they propound a formula that correlates the relationship of the transverse diameter of the heart with variables of height, weight, and age, and show that this formula is capable of mathematical verification.

Betty A. R. Student. Intercollegiate swimming; aged 20; ht. 62½ in.; wt. 125 lbs. Transverse diameter. 10.7 cm. E. K. G. normal. Esophagram—no distortion.

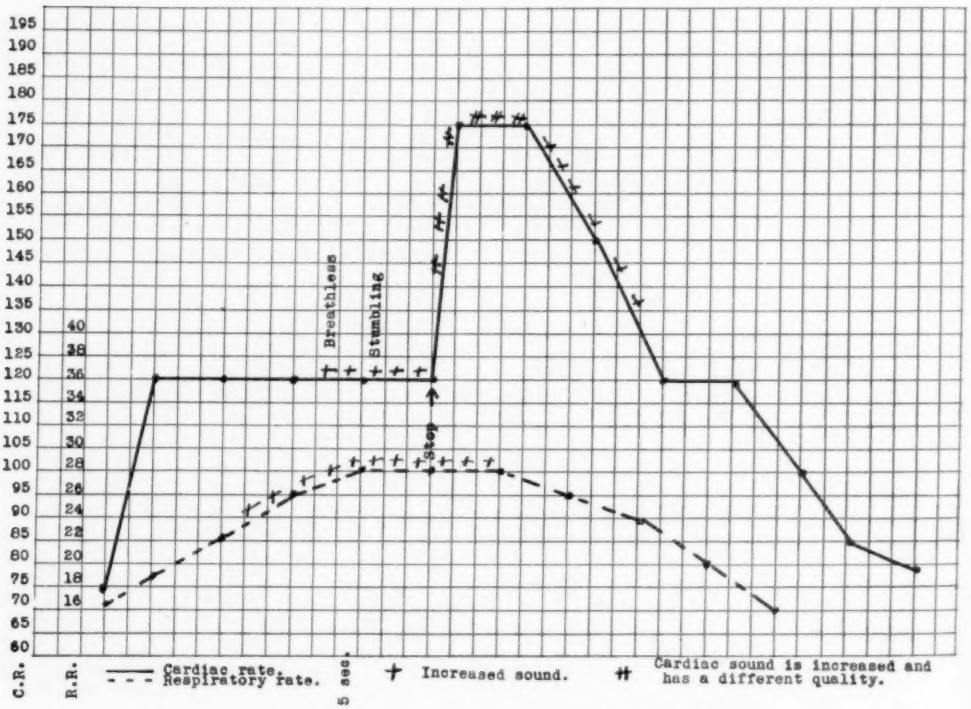


CHART 2. A fair test in an athlete out of training. The working rate is well maintained but there is a pause at the height of the reaction to rest. There is a short plateau of rest (15 seconds).

The fact is that the transverse cardiac diameter in an individual free from cardiac disease bears a constant relationship to one or more body measurements that can be readily and accurately obtained, and that this relationship can be advantageously used to predict the probable transverse diameter of the heart of any given individual, even predicting in which individual the heart by lying transversely will increase the diameter of its shadow, and in which individual by hanging vertically will diminish the diameter of its shadow.

Hodges and Eyster have employed their formula (the transverse diameter of the heart $= +0.1094 \times$ age $+ 0.8179 \times$ weight $- 0.1941 \times$ height) in drawing up a table from which one can predict the normal transverse diameter of the heart of the individual with an error of less than 5 mm. This table was used in predicting the normal transverse diameter of the hearts of the athletes that we examined.

Having satisfied ourselves that we could determine when a heart was enlarged, and finding this enlargement was limited to a small percentage of

Ernest L. B. Student; aged 23; ht. 70 in.; wt. 160 lbs.
Transverse diameter. 11.5 cm. Esophagram—no distortion. Double mitral murmur and thrill. E. K. G. normal.
Well compensated mitral disease.

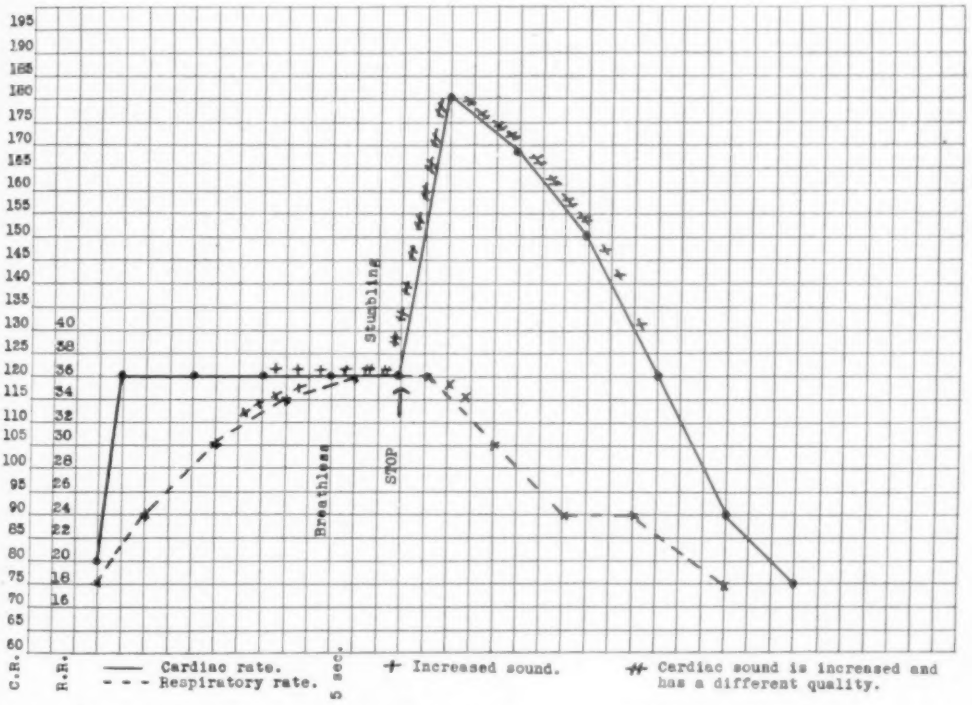


CHART 3. A good test in spite of physical signs of mitral disease of the heart.

athletes not engaged in any special sport, we could expect to find an explanation of the hypertrophy in the heart itself.

To our surprise there did not seem to be any relationship between cardiac damage, the size of the heart, and the individual's athletic prowess.

It was noted that cardiac hypertrophy due to the strain of exercise upon slightly damaged hearts was established during the period of athletic exertion in high school, and that an additional increase in size was rarely noted when the athletes were followed through their four years of university competitive sports.

To determine that a heart is normal requires a very complete cardiac examination and we have found the following data necessary:

1. The type of athletic sport that the individual is engaged in.
2. The height, weight, and age.
3. The transverse diameter of the thorax.
4. The transverse diameter of the heart shadow as shown by the teleroentgenogram or orthodiagram.
5. The predicted normal transverse diameter as given for the individual's height, weight, and age.

Geo. W. H. Student; aged 24; ht. 73½ in.; wt. 187 lbs.
Transverse diameter. 16.5 cm. Esophagram—distorted. E. K. G. Left preponderance and impaired conduction.
Rheumatic fever 1936 and 1937. Mitral disease—poorly compensated.

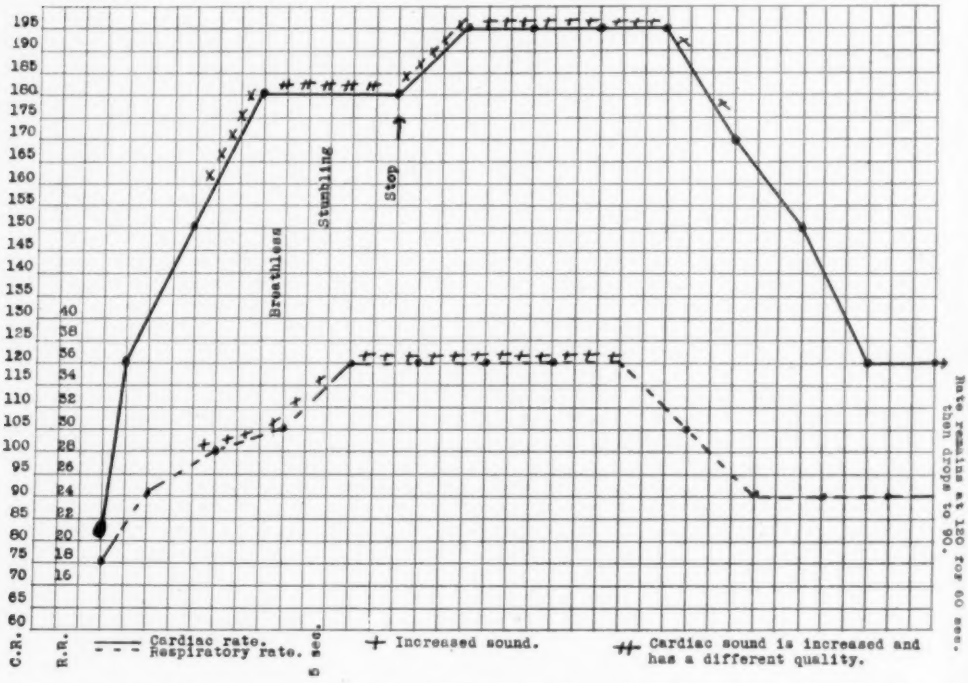


CHART 4. A lack of control of the working rate of the heart in a badly damaged heart due to valvular disease. Note plateau of rest.

6. A film taken of the position of the esophagus in the right oblique lateral position, to determine the size of the posterior chamber of the heart (left auricle) as shown by its indentation of the esophagus, and an anteroposterior film to show lateral displacement of the esophagus by the same chamber, the films being taken immediately after the swallowing of a mouthful of barium paste. We found that any enlargement of the left auricle first compresses the esophagus, and then displaces it laterally to the right.

Any enlargement of the left ventricle of sufficient size to rotate the heart displaces the esophagus laterally to the left.

7. The blood pressure should be taken.*

8. Palpable thrills have to be noted.

9. The presence of a murmur has to be sought for in the upright and in the prone positions after rest and during exercise, and its character and position in the cardiac cycle noted.

Robert P. Student; aged 20; ht. 72½ in.; wt. 138 lbs.
Transverse diameter. 10.5 cm. No murmurs. Esophagram—no distortion. E. K. G. partial heart block. Auricular fibrillation.
No cardiac history.

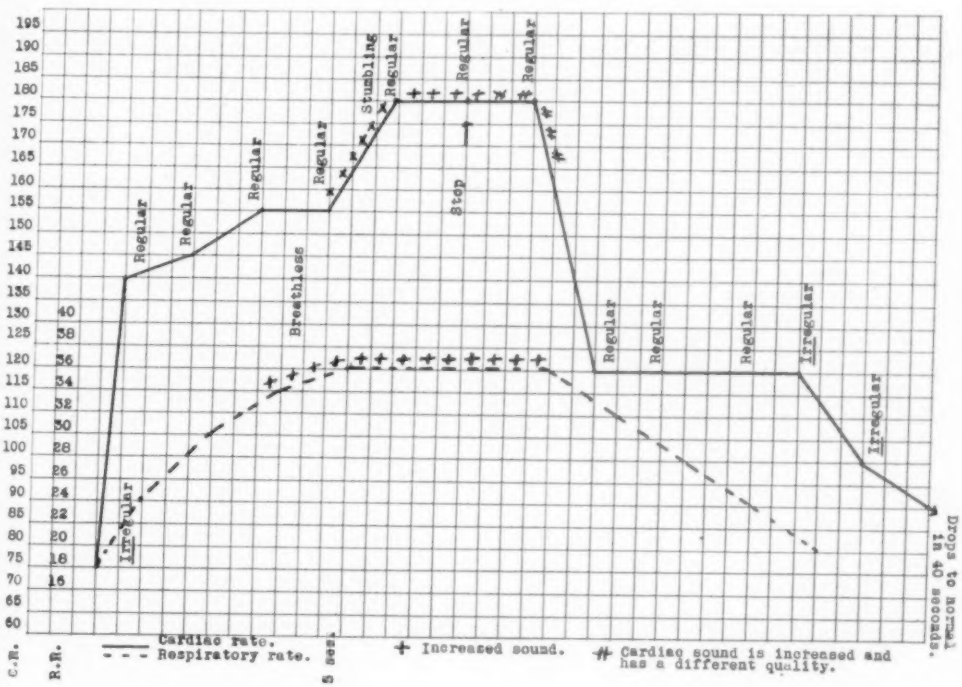


CHART 5. A lack of ability to control the resting rate of the heart due to interference with conductivity within the heart. Note plateau of rest. Also note that the heart rate becomes regular while under stress.

10. Special attention has to be given to the cardiac first sound at the apex and the second aortic sound over the aortic area.

11. An electrocardiogram should be studied.

12. Each patient should be put through a cardiac fatigue test which is usually spoken of as a cardiac function test. The purpose of the usual cardiac function test is to produce cardiac fatigue and estimate how quickly the heart recovers from it.

* All the athletes tabulated in these data had a blood pressure within normal range.

As it is not practical to demand a complete cardiac examination of all high school athletes, we have developed a cardiac function test that corresponds in its results with the rest of the cardiac examination and that will help to identify the individual whose heart is embarrassed, for it is evident that cardiac examinations carried out in high school and even in the university overlook a small per cent of hearts that are damaged.

We are led to believe that strenuous physical exercise produces no change in the normal heart and that the response of the slightly damaged heart to

Clyde E. B. Student; aged 22; ht. 66½ in.; wt. 140 lbs. Nonathletic. Transverse diameter. 11 cm. Esophagram—no distortion. E. K. G. Hypersensitivity of myocardium.
Vagohypotonia—fainting, sweating, flushing, etc.

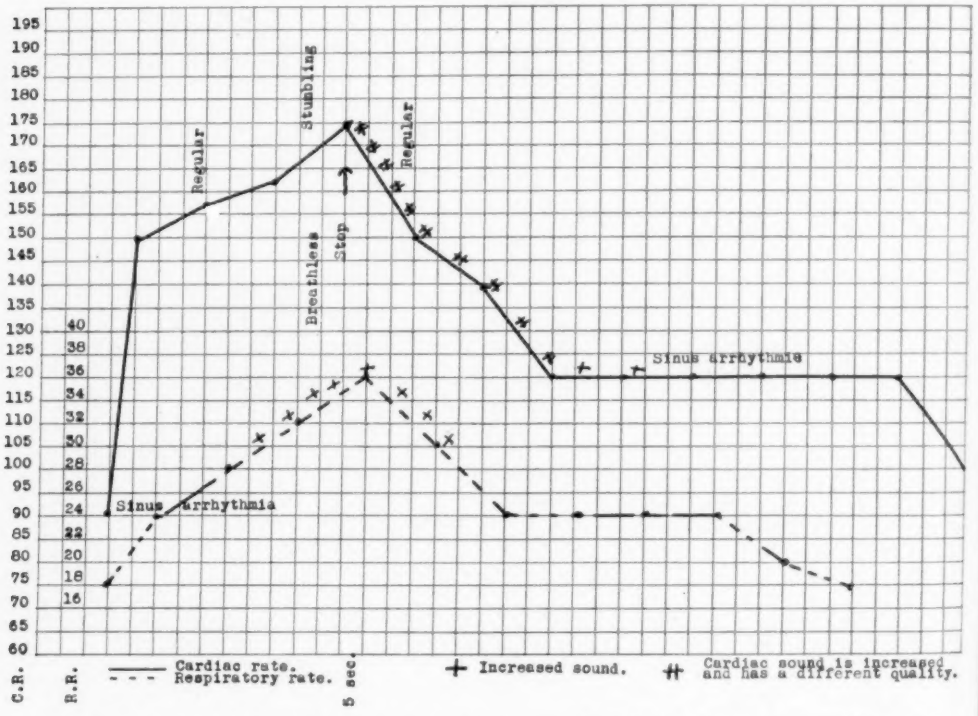


CHART 6. Lack of control of rate, due to vagohypotonia. Note that evidence of Starling's cycle does not appear until rest. Note plateau of rest. Also note that rate becomes regular under stress.

this same amount of exertion is hypertrophy. As this is an abnormal condition that is not desirable, great care should be exercised early in life to guard these individuals against the hazard of too great physical exertion.

THE CARDIAC FUNCTION TEST

A cardiac function test is simply a test to determine how an individual's heart responds to work, and should be carried to the point of fatigue in each instance.

In dealing with the age group of high school and university students where there are some individuals trained to long continued athletic exercise, and other individuals having no bodily training at all, a standard test is necessarily futile, so it became necessary to evolve a test that could be carried out to the point of fatigue in each individual tested. This was done by bandaging a Bowles' stethoscope, with a 5 cm. bowl, and six feet of rubber tubing over the precordia. Then the individual was exercised in the squatting, or sitting-up exercise which quickly fatigues even the trained

Geo. R. Track (running); aged 23; ht. 74 in.; wt. 177 lbs.
Transverse diameter. 14.3 cm. Esophagram—no distortion. E. K. G. Normal.
No murmurs.

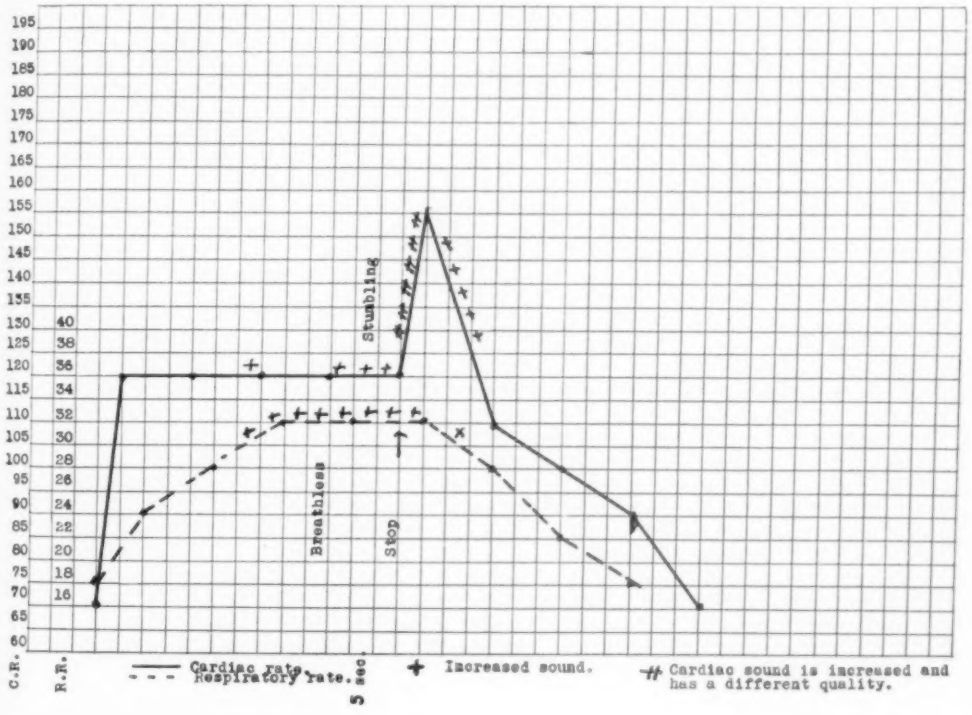


CHART 7. A good test in a normal, well trained heart.

athlete. This was carried to the point of exhaustion in every instance—exhaustion being indicated by a flushed face, breathlessness, and stumbling.

The pulse was taken during rest before exercise, and for every 10 seconds during exercise, with five-second intervals to record the rate—this making a notation of the cardiac rate at every 15 seconds. These records were reduced to graphic charts, and after the test had been used in several hundred instances a number of interesting phenomena were observable.

The heart is a positive pressure pump which most precisely adapts itself

to the constantly changing requirements of the body. This adaptation consists, as in any other pump, in changing the strength of each contraction and in changing the frequency of the contractions, responding thus to the demands of the systemic circulation by both the strength of the heart beat and by the rate of the heart's contractions.

The regulation of the heart rate is a function of the nervous system, whereas the adaptation of the heart for the purpose of a greater output is intrinsic in the heart itself—the heart being able to increase its normal output many times, by increasing the tonicity of its muscle and providing for

Geo. R. After 1/100 gr. atropine sulphate—hypo.

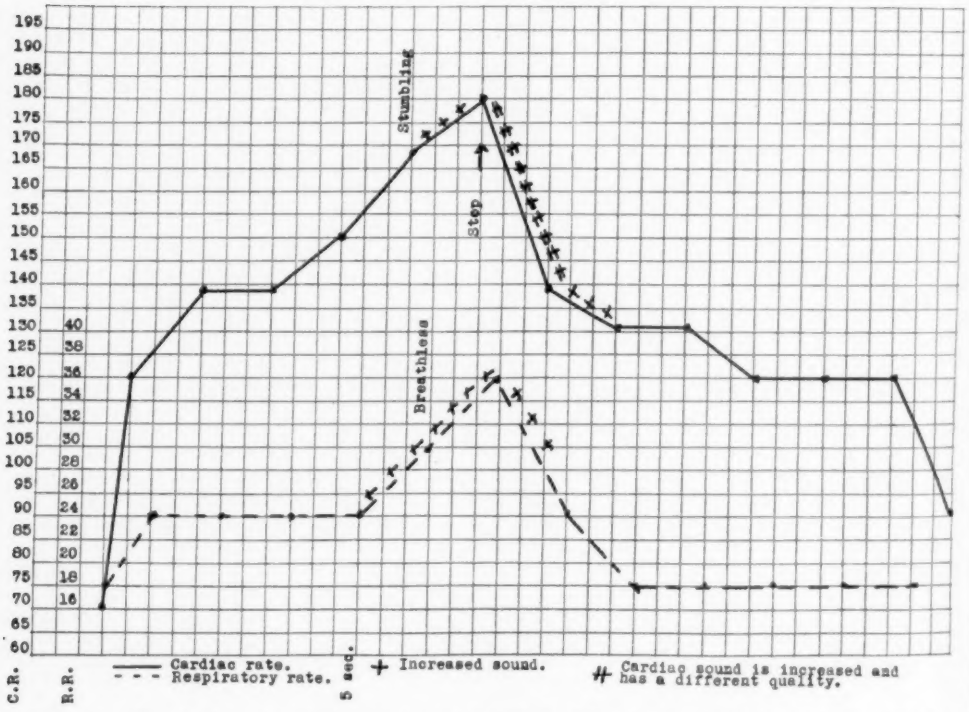


CHART 8. No. 7 after the administration of atropine. Note how closely it resembles No. 6 with vagohypotonia.

dilatation of the chambers by the lengthening of its muscle fiber. These changes take place from beat to beat in answer to the requirements brought about by changes in the systemic circulation.

Out of the great mass of investigative material that has been published in connection with the heart rate and cardiac output, we wish to call attention to the three following factors:

First, it was suggested by Marey, and has been called Marey's Law, that the heart rate has an inverse relation to the blood pressure, that is, the higher the pressure the lower the rate.

Heymans and Ludwig have shown that the slowing of the pulse is due to the effect of an increase in blood pressure on the nerve ends in the aorta. Later, Hering added the effect of this same pressure in the carotid sinus, both acting reflexly on the vagus to slow the rate of the heart.

Second, Starling and others have shown that the essential factor governing the output of the heart is the inflow; that within physiological limits the force of the heart's contraction depends upon the extent to which the heart muscle has been stretched by incoming blood; that by increased tonicity

C. A. L. Inactive; aged 27; ht. 72½ in.; wt. 204 lbs.
Transverse diameter. 12 cm. Esophagram—no distortion. E. K. G. Normal.
No murmurs.

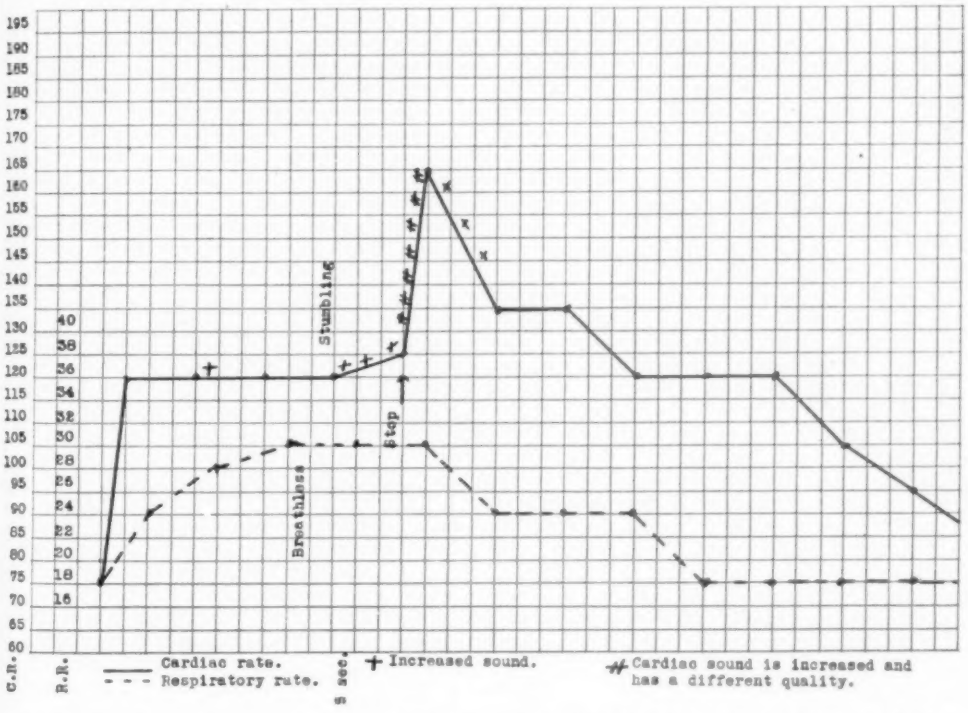


CHART 9. A poor test in a fat, inactive individual. Working plateau is not fully sustained. There is a resting plateau of 30 seconds.

(strengthening of beat), and dilatation (lengthening of cardiac muscle fiber), the heart increases its output at the demand of an increased inflow.

Third, the rate of the heart responds to venous pressure. As shown by Bainbridge, the heart reacts to an increased venous return, that is, dilatation of the great veins entering the right auricle and the right auricle itself, by acceleration of the rate of the heart. This acceleration is evidently reflex in character—the reflex path running to the vagi and also to the accelerator nerves, the acceleration being the result of a reciprocal action between the two sets of nerves, but being due chiefly to diminution of the vagus tone.

Nowhere, however, is there mention of any controlling factor of rate above the resting level at 75 beats per minute. Bowen, in his work on bicycle riders, briefly mentions that the rate tends to reach a plateau during sustained exertion. MacWilliam's work on the effect of chloroform on the cardiac rate in cats mentions that after the initial excitement the rate tends to stabilize at a high level. No deductions were drawn from either of these observations.

In view of these brief facts, taken from many, pertaining to the heart, let us look at the results of our fatigue test in a normal patient. His rate, at

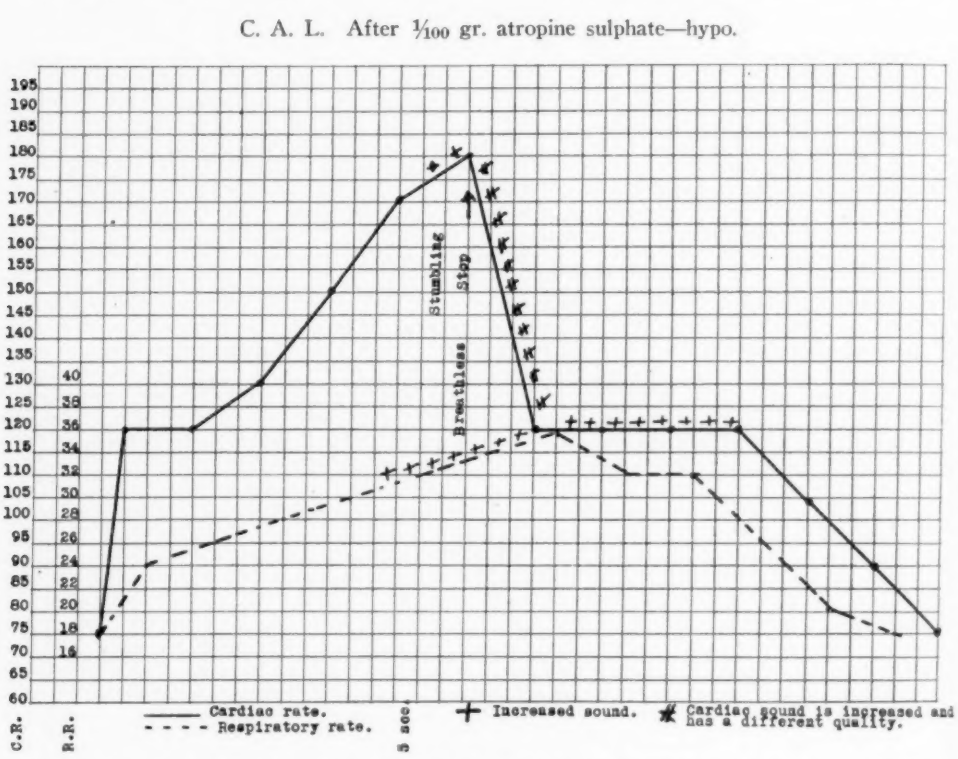


CHART 10. No. 9 after the administration of atropine. The graph more closely resembles that of vagohypotonia.

rest, is in the near neighborhood of 75 beats per minute, which is the result of a nice balance between the accelerator and depressor nerves of the heart.

Immediately on exercise, usually starting within one cardiac cycle, there is a rapid rise in rate due to the institution of the mechanism of the Bainbridge reflex. In well-trained athletes with normal hearts there may be a pause of two or three cardiac cycles before the increase in rate is inaugurated. This acceleration is due chiefly to the diminution of the vagus tone, and slightly to the increased accelerator tone—this being brought about reflexly from the dilatation of the mouths of the greater veins of the right auricle

with venous blood. Instead of this acceleration continuing indefinitely to the point of exhaustion of the heart, we find by our test that this acceleration continues until, within five seconds, it reaches 120 beats per minute, or in the very close neighborhood of 120 beats per minute, and remains at this rate until the individual becomes exhausted. Evidently the rise in rate is stopped by the working of the modern conception of Marey's Law (the increase in aortic and carotid pressure reactivating the depressed vagus function), bringing about a new equilibrium that forms a normal working pulse rate of 120

Arthur D. Inactive for 2 years; aged 22; ht. 76 in.; wt. 165 lbs.
Transverse diameter. 11.3 cm. Esophagram—no distortion. E. K. G. Normal.
No cardiac murmurs.
Vagohypotonia—fainting, sweating, flushing, etc.

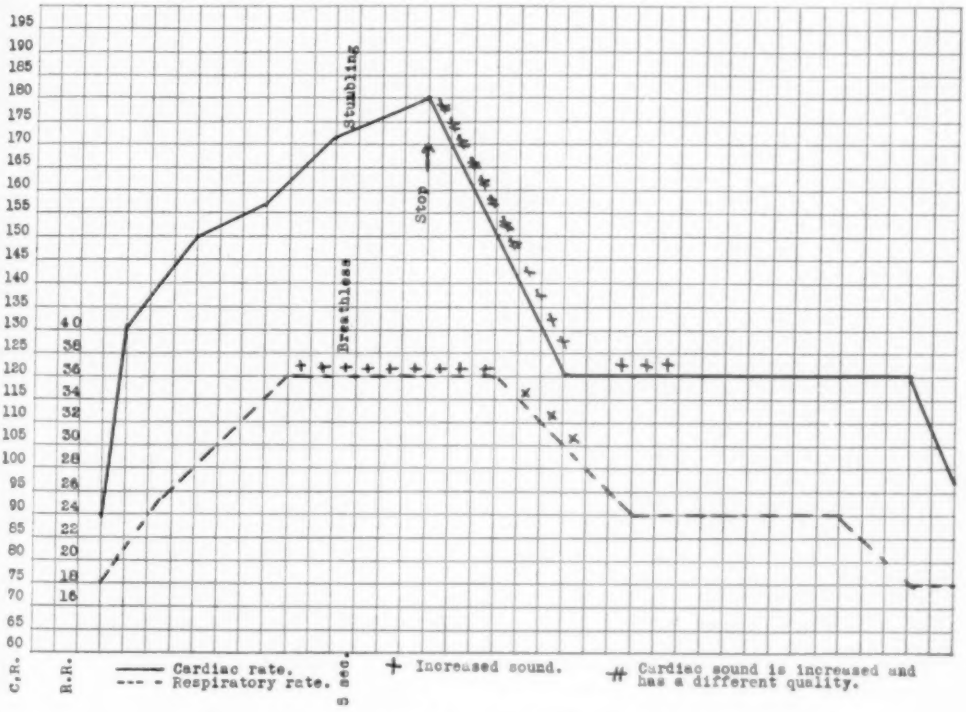


CHART 11. A bad test in a vagohypotonic individual.

beats per minute. We know that it is the vagus action because atropine abolishes it.

The onset of Starling's cycle is indicated by a suddenly marked increase in the cardiac first sound and sometimes a change in quality of sound, as well.

After the individual becomes exhausted and is allowed to rest, then there is another immediate rise in rate, reaching its maximum within five seconds of time.

In untrained individuals this can be a rise of from 30 to 50 beats per minute. In the trained individual, this rise is usually from 10 to 30 beats per minute. Unless the heart is definitely fatigued this increase in rate may not be present. The rise in rate is brought about by the sudden ceasing of the working of Marey's Law, that is, it is brought about by the sudden drop in blood pressure in the aorta and carotid sinus, allowing the accelerator influences free play. The vagus now slowly regains its tone, and from the highest point the rate slowly drops, reaching a normal rate from 60 to 80 seconds after the cessation of exercise.

Arthur D. After 1/100 gr. atropine sulphate—hypo.

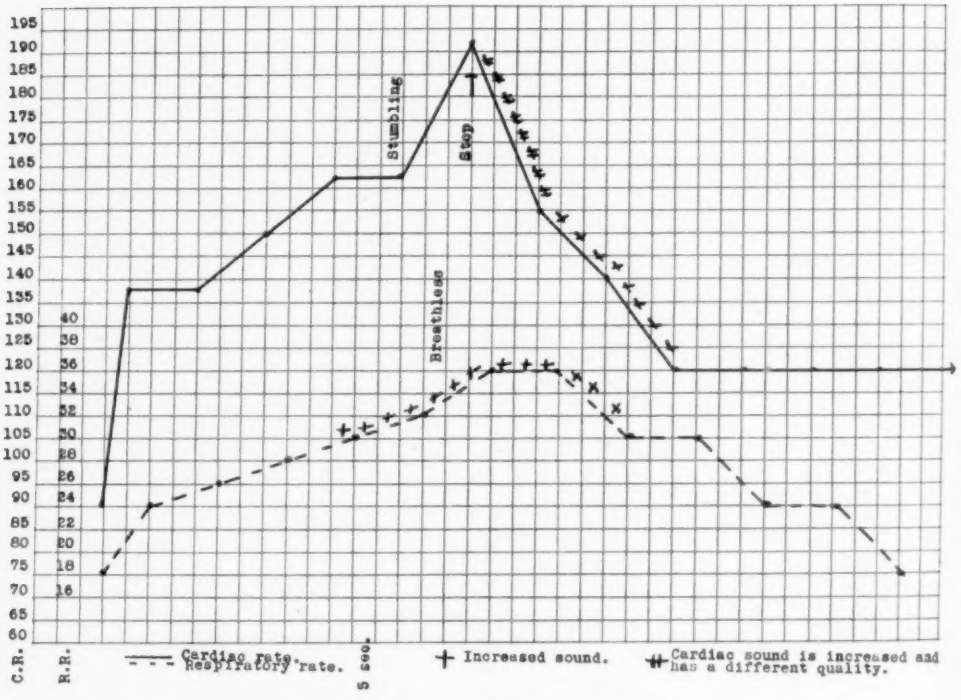


CHART 12. No. 11 after the administration of atropine. Note how little change atropine produces, due to the fact there is but little vagus control to be lost.

This description covers the reaction of the heart to work in the normal individual. We have encountered three types of individuals, however, that do not respond in this way to exercise.

First is the *vagohypotonic* individual. Vagus tone is essentially of a protective nature and its development depends greatly upon the requirements of the individual. In some individuals this protective tone of the vagus (although there is some doubt that the vagus alone is involved) is below par, and this autonomic imbalance is the cause of many functional disturbances that are grouped together under the symptom complex of vago-

hypotonia. The vagohypotonic individual has no normal resting cardiac rate; it may be anywhere between 90 and 110.

In the vagohypotonic individual, with the beginning of exercise, the cardiac rate responds to the Bainbridge reflex, and at the point where it should meet the vagus control, i.e., 120 beats per minute, there is no check upon its velocity, and it increases to an exceedingly high rate, causing the individual quickly to become exhausted. On rest, this individual does not have the rise in rate which in the normal individual comes with the release of the vagus from the stimulation of the distended aorta and carotid sinus, but that control being absent and the rate having risen to an uncontrolled

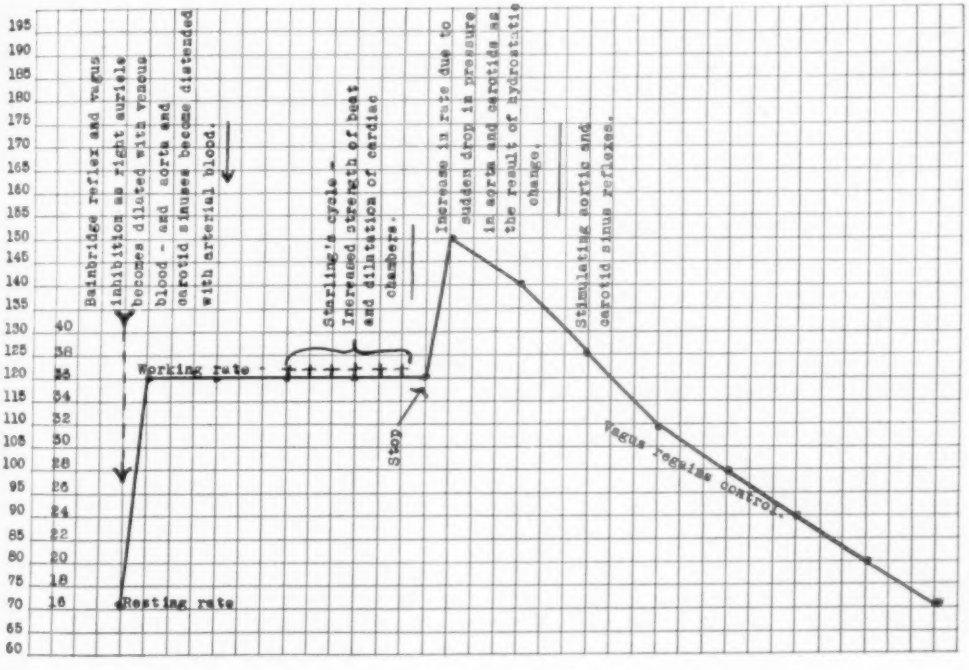

Bainbridge reflex and vagus inhibition as right auricle becomes dilated with vagous blood - and aorta and carotid sinuses become distended with arterial blood.
Starling's cycle - Increased strength of beat and dilatation of cardiac chambers.
Increase in rate due to sudden drop in pressure in aorta and carotids as the result of hydrostatic change.
Stimulating aortic and carotid sinus reflexes.
Working rate
Stop
Vagus regains control.
Resting rate

CHART 13. Possible physiological explanation of normal record.

level (sometimes as high as 240 beats per minute), the rate starts dropping from its highest point at the ceasing of exercise. However, when the slowly dropping rate reaches 120 beats per minute it is held on a plateau at this level for an indefinite length of time, evidently allowing for certain readjustments in the circulation and within the heart itself, probably made necessary by the extreme rate. After the pulse has been held at this plateau of 120 beats (which we designate the plateau of rest and which strangely coincides with the plateau of the working rate of the heart), from 30 to 80 seconds or more, it slowly seeks its previous resting rate. The administration of atropine has no effect on the test of a vagohypotonic individual.

The second type of individual that does not respond normally to exercise is the individual with a myocardium so damaged that there is no longer a normal conductivity of impulses through it. The reaction in cardiac rate in this type of individual to cardiac fatigue is exactly the same as that of the vagohypotonic individual, including the plateau of rest during the period of recovery, at 120 beats per minute.

The third type of individual that does not respond normally to exercise is the individual with valvular defects. When these defects are well compensated for and can maintain a normal circulatory response to exercise, the heart gives a perfectly normal test; whereas individuals with poorly compensated valvular defects, who, in spite of their increased rate on exercise, cannot maintain an increased output (for an acceleration of the pulse rate does not indicate an increased cardiac output, but may indicate merely a demand for such an increase), give an abnormal test. There is a lack of increased intra-arterial pressure in the aorta and carotids, due to a faulty cardiac output, so that no vagus control is initiated to establish a normal working level of the pulse. In many cases this is probably aided by damaged conductivity of the heart muscle. The rate continues to increase until the individual is exhausted and then drops as in the other two instances, again establishing a plateau of rest at 120 beats per minute, allowing the heart and circulation to readjust themselves after having maintained an excessive cardiac rate.

The important elements in the graphic charting of the cardiac rates maintained by the heart during exercise are:

The ability of the heart to maintain a normal plateau of working rate at 120 beats a minute.

The ability of the heart promptly to increase its rate on rest and then as promptly to decrease this rate.

A plateau during the resting period indicates poor cardiac function and the degree of disability is indicated by the length of time this plateau is maintained.

We are fully aware that this test is a crude method of measuring the cardiac events described above and that instruments of precision applied to the test may show that the graphs do not run so smoothly, but the test is simple and easily done (this is essential in examining large groups), and is, in the main, accurate in its demonstration of the heart's ability to function properly.

This year we have examined 100 athletes carrying out the complete cardiac examination. Seventeen hearts were found to exceed their predicted transverse diameter. Sixteen of these showed evidence of cardiac damage on physical examination or electrocardiographic examination, or both. The remaining one showed marked evidence of vagohypotonia. Of the 17 with cardiac enlargement, 12 gave a function test that was poor or bad, while five gave function tests that could be graded from fair to good.

Among the 83 athletes with hearts within the predicted measurements, 80 gave tests rating from fair to good, while three (all showing evidence of vagohypotonia) were rated poor.

Conclusions

We feel that the presence of cardiac hypertrophy in a group of athletes points to the ineffectiveness of the cardiac examination given the athletes.

A complete examination of the heart is expensive and time-consuming, and requires an especially trained personnel.

We feel that the function test described above will allow an examiner to appreciate the heart's reaction to physical exertion by its changes in rate, and by the changes in the sounds produced by its contractions.

BIBLIOGRAPHY

1. Williamson, C. S.: The effect of exercise on the normal and pathological heart, Am. Jr. Med. Sci., 1909, cxxxviii, 549.
2. Shattuck, G. C.: Cardiac enlargement, Boston Med. and Surg. Jr., 1916, clxxiv, 384.
3. Josephs, D. R.: Ratio between the heart weight and body weight in various animals, Jr. Exper. Med., 1908, x, 521.
4. Deutsch, F., and Kauf, E.: Heart and athletics (Translation by L. M. Warfield), 1927, C. V. Mosby Co., St. Louis, Mo.
5. Eyster, J. A. E.: Determination of cardiac hypertrophy by roentgen-ray methods, Arch. Int. Med., 1928, xli, 667.
6. Hodges, Fred J., and Eyster, J. A. E.: Estimation of transverse cardiac diameter in man, Arch. Int. Med., 1926, xxxvii, 707.
7. Peabody, F. W.: Vital capacity of lungs in heart disease, Med. Clin. N. Am., 1921, iv, 1655.
8. Blumer, George: Bedside diagnosis, Vol. II, 1928, W. B. Saunders, Philadelphia, p. 545.
9. Smith, H. L.: "Athletic heart," an unfortunate term, Proc. Staff Meet. Mayo Clin., 1935, x, 122.
10. White, S. A., and McGuire, P.: Vital capacity in citizens' military training camp, Arch. Int. Med., 1925, xxxvi, 355–365.
11. Peacock, T. B.: On some of the causes and effects of valvular disease of the heart, 1865, J. Churchill and Sons, London.
12. Da Costa, J. C.: Physical diagnosis, 1916, W. B. Saunders, Philadelphia.
13. Bedford, Evan D.: The size of the healthy heart and its measurement, Lancet, 1931, ii, 836.
14. Messinger, E.: The estimation of cardiac function by simple clinical methods, Ann. Int. Med., 1937, x, 986.
15. White, P. D.: Heart disease, Macmillan Company, New York, pp. 454–479.
16. Cabot, Richard: Facts on the heart, 1926, W. B. Saunders, Philadelphia.
17. Wood, J. E., and White, P. D.: Interpretation of mitral diastolic and aortic systolic murmurs, Med. Clin. N. Am., 1923, vii, 729.
18. Held, E., Goldbloom, A. A., and Rittenberg, L. M.: Mitral stenosis with special reference to buttonhole mitral stenosis, Med. Clin. N. Am., 1931, xiv, 1311.
19. Paterson, R., and Paterson, E.: Experiment on the effect of exercise on the heart in athletes, Am. Jr. Roentgenol., 1935, xxxiv, 158.
20. Levene, G., and Reid, W. D.: A chart for the differential diagnosis of cardiac enlargement by means of roentgen ray, Am. Heart Jr., 1931, vii, 380.

21. EYSTER, J. A. E.: The size of the heart in normal and in organic disease, Radiology, 1927, viii, 300–306.
22. GOLDEN, R.: Diagnostic roentgenology—measurement of the cardiovascular system, 1938, Thomas Nelson and Sons, N. Y., p. 209.
23. DANZER, C. S.: The cardiothoracic ratio, an index of cardiac enlargement, Am. Jr. Med. Sci., 1919, clvii, 513.
24. BARDEEN, C. R.: Determination of the size of the heart by means of the x-rays, Am. Jr. Anat., 1918, xxiii, 423.
25. STEINHAUS, A. H.: Chronic effects of exercise, Physiol. Rev., 1933, xiii, 103.
26. BAINTON, J. H.: Silhouette of the heart and the aortic arch, Am. Heart Jr., 1932, viii, 616.
27. STEINHAUS, A. H., KIRMIZ, J. P., and LAURITSEN, K.: Studies in the physiology of exercise; chronic effects of running and swimming on hearts of growing dogs as revealed by roentgenography, Am. Jr. Physiol., 1932, xcix, 487.
28. HERRMANN, G. R.: The heart of the racing greyhound, Proc. Soc. Exper. Biol. and Med., 1926, xxiii, 856.
29. ROESLER, HUGO: A roentgenological study of the heart size in athletes, Am. Jr. Roentgenol., 1936, xxxvi, 849.
30. ANREP, G. V.: Lane medical lectures: Studies in cardiovascular regulation, 1936, Stanford University Press.
31. HEYMANS, C., and LADON, A.: Recherches physiologiques et pharmacologiques sur la tête isolée et le centre vague du chien, Arch. internat. de pharmacod., 1925, xxx, 415.
32. HERING, H. E.: Compression of carotid artery, München. med. Wchnschr., 1923, vii, 1287. Die Karotissinusreflexe auf Herz und Gefässe, 1927, Theodor Steinkopff, Dresden.
33. HEYMANS, C.: Arch. internat. de pharmacod., 1929, xxxv, 269.
34. BOWEN, W. P.: Changes in heart rate, blood pressure, and duration of systole resulting from bicycling, Am. Jr. Physiol., 1904, xi, 59.
35. FRANK, OTTO: Zur Dynamik des Herzmuskels, Ztschr. f. Biol., 1895, xxxii, 370.
36. GROLLMAN, ARTHUR: The cardiac output of man in health and disease, 1932, Charles C. Thomas, Springfield, Illinois.
37. WIGGERS, C. J.: Physiology in health and disease, 1937, Lea and Febiger, Philadelphia.
38. HEWLETT, A. W.: Pathological physiology of internal diseases, 1924, D. Appleton and Company, New York.
39. MCDOWALL, R. J. S.: Clinical physiology, 1927, D. Appleton and Company, New York.
40. MCDOWALL, R. J. S.: A vago-pressor reflex, Jr. Physiol., 1924–25, lix, 41.
41. MACWILLIAM, J. A.: On the influence exercised by the central nervous system on the cardiac rhythm with an inquiry into the action of chloroform on that rhythm, Proc. Roy. Soc., 1893, liii, 465.
42. NEWBURGH, L. H., and MEANS, J. H.: The blood flow in a patient with double aortic and double mitral disease, Jr. Pharmacol. and Exper. Therap., 1915, vii, 441.
43. MEEK, W. J., and EYSTER, J. A. E.: Cardiac size and output in man during rest and moderate exercise, Am. Jr. Physiol., 1922, lxiii, 400.
44. BAINBRIDGE, F. A.: The influence of venous filling upon the rate of the heart, Jr. Physiol., 1915–16, l, 65.
45. GASSER, H. S., and MEEK, W. J.: A study of the mechanisms by which muscular exercise produces acceleration of the heart, Am. Jr. Physiol., 1914, xxxiv, 49.
46. MCDOWALL, R. J. S.: A right auricular pressor reflex, Jr. Physiol., 1934, lxxxi, 5.
47. MCDOWALL, R. J. S.: Nervous control of blood vessels, Physiol. Rev., 1935, xv, 98.
48. HERING, H. E.: Ueber die Beziehung der extracardialen Herznerven zur Steigerung der Herzschlagzahl bei Muskelthätigheit, Arch. f. d. ges. Physiol., 1895, lx, 429.
49. HEYMANS, C., and LADON, A.[31]
50. MANSFELD, G.: Die Ursache der motorischen Acceleration des Herzens, Arch. f. d. ges. Physiol., 1910, cxxxiv, 598.

51. Lewis, Sir Thomas: Diseases of the heart described for practitioners and students, 1937, Macmillan Company, London.
52. Christian, H. A.: The diagnosis and treatment of diseases of the heart, 1935, Oxford University Press, London.
53. Patterson, S. W., Piper, H., and Starling, E. H.: Jr. Physiol., 1914, xlviii, 465.
54. Starling, E. H.: Harveian Oration: Wisdom of the body, Lancet, 1923, ii, 865.
55. Stine, D. G.: The meaning of athletic heart among university athletes, Proceedings of the eighteenth annual meeting of the American Student Health Association, December, 1937, Chicago.
56. Stine, D. G.: The effect of work upon the heart, Jr. Missouri State Med. Assoc., 1938, xxxv, 443–446.

ROENTGEN PROCEDURES USEFUL IN CARDIAC DIAGNOSIS *

By Fred Jenner Hodges, M.D., *Ann Arbor, Michigan*

Bluntly stated, the medical profession's ability to diagnose diseases of the heart greatly outweighs its ability to successfully treat patients with cardiac disorders. This discrepancy has served as a stimulus to even further development in the field of cardiac diagnosis based upon the belief that rational and successful therapeutic efforts can be developed only upon a broader and more complete understanding of the subject.

Roentgen-rays, because of their unique ability to penetrate successfully the various tissues of the body, offer a means of observing the heart which has appealed to physicians ever since the year of Roentgen's discovery. In common with progressive development in electrocardiography, new adaptations of the roentgen-ray method to the study of heart disease have been described from year to year, until in the aggregate there has developed a considerable literature devoted to this particular subject. It is difficult to evaluate rigidly the importance of individual procedures since the efficacy of these varies greatly, depending upon the type of cardiac abnormality under consideration. Roentgen-ray examination alone, however specific and detailed, never constitutes adequate study in any individual case, although it may on occasion be more helpful than any other single procedure.

It is wise to remember that under some circumstances, which unfortunately are not uncommonly encountered in patients with cardiac disease, all roentgen-ray methods of study may be rendered entirely ineffectual. If the heart is surrounded by accumulations of pleural fluid, or lung rendered abnormally dense as the result of disease, or if its roentgen shadow is obscured because of abnormal elevation of the diaphragm, shift of the mediastinum, vertebral deformity, great adiposity, herniation of abdominal structures through the diaphragm, or other comparable situations it is obviously impossible for roentgen procedures to succeed. Certain diagnostic procedures depending upon the use of roentgen-rays require a degree of cooperation on the part of the subject being examined which the patient's condition may not permit. Some of the more elaborate procedures require, in addition to wide experience and great ingenuity on the part of the examiner, highly specialized equipment, which it is impracticable to maintain in any roentgen laboratory where the demands for highly specialized cardiac examination are infrequent. Some of the more uncommonly employed methods of studying the heart require a great deal of time and effort on the part of the examiner, and may be properly considered experimental rather than clinically practicable investigations. An opportunity to observe casually

* Read at the New Orleans meeting of the American College of Physicians March 28, 1939.

From the Department of Roentgenology, University of Michigan.

the shadow cast by the heart and its great vessels as shown in a simple roentgenogram of the chest in frontal projection is satisfying to the cardiologist, if nothing more, for many of the observations he is able to make without such assistance are less rapid and more indirect. Good judgment is required in order to determine which patients can be advantageously studied with roentgen-ray methods of a more highly specialized nature. Such decisions depend to a very large extent upon findings observed in a preliminary survey of the entire chest, although many other indications are to be found in the patient's history and among findings obtained on searching physical examination.

Preliminary Scout Roentgenogram of Chest

Situations responsible for insurmountable technical difficulties certain to defeat accurate roentgen-ray examination of the heart are readily detected by cursory inspection of a scout film. Figures 1 and 2 represent circum-

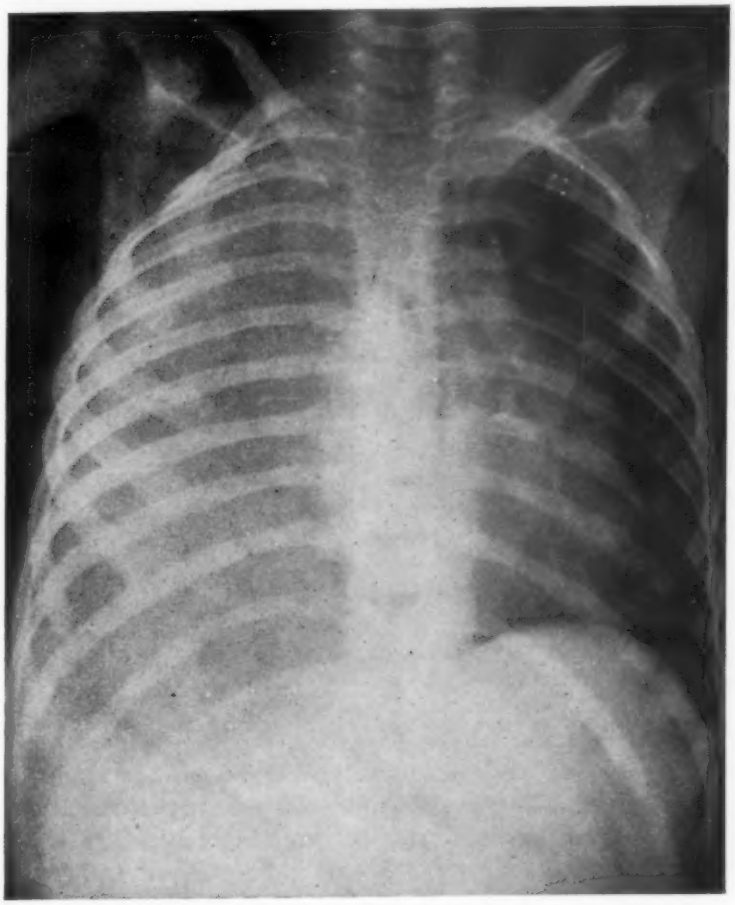


Fig. 1. Massive pleural effusion obliterating right cardiac border.

stances which operate to render the shadow of the heart indistinguishable from surrounding structures. In the first of these the entire right chest has been rendered uniformly opaque by the accumulation of pleural fluid, whereas in the second example chronic obstruction of the main bronchus on the left followed by pulmonary atelectasis and an extreme degree of bronchiectasis serves to conceal the heart which has been displaced sharply to the

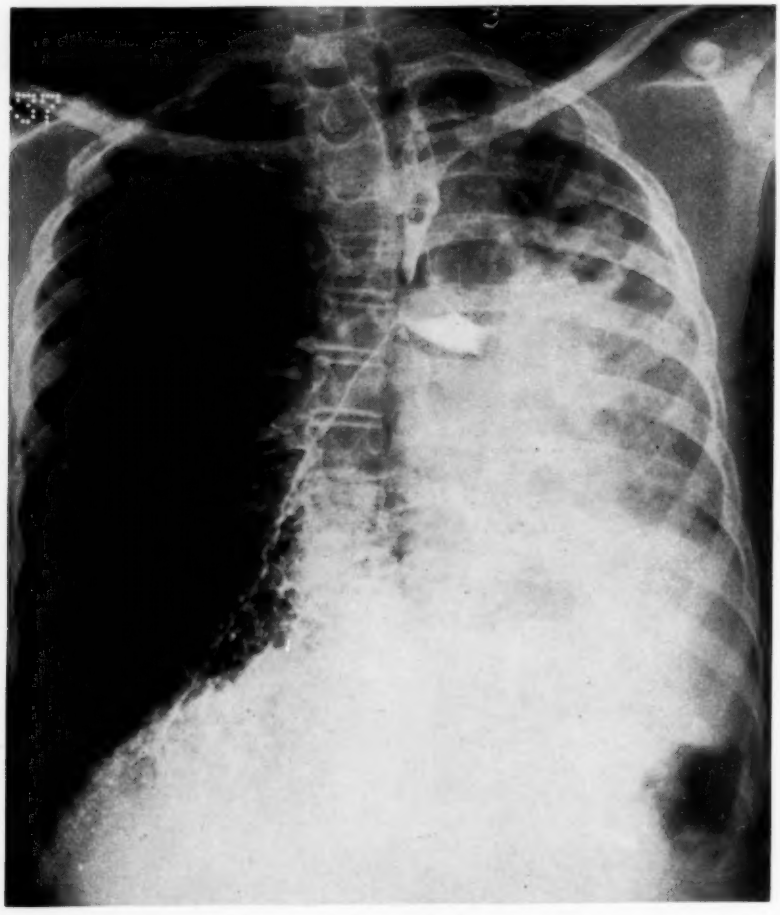


FIG. 2. Obstruction of the left bronchus producing bronchiectasis, atelectasis, and mediastinal shift to the left with resultant obliteration of cardiac contours.

affected side as the result of compensatory emphysema in the contralateral lung. Figure 3 shows a very obviously enlarged cardiac shadow. In this instance it would seem wise to determine, with whatever degree of accuracy is possible, the extent to which this patient's heart has been enlarged. In figures 4 and 5, the contours of the heart are seen at first glance to deviate materially from the expected shape of the cardiac silhouette. Remarkable

bilateral broadening of the shadow just above the diaphragm, and obvious total enlargement of the shadow, at once suggest the likelihood of underlying pericarditis with effusion; a point which might be subjected to further clarification by additional fluoroscopic and roentgenographic study. In figure 5 the abnormality in shape suggests a congenital malformation which might well be profitably studied by far more elaborate examination by roentgen methods.

FIG. 3. Marked cardiac enlargement.

These few illustrations will serve to show how a single scout film of the chest may quickly convince the examiner that further roentgen-ray study of the heart in a given case is apt to be profitless, or on the other hand stimulate him to employ further, more detailed, roentgen procedures.

CARDIAC SIZE AND VOLUME DETERMINATION

Without doubt the most commonly employed and withal the most generally profitable utilization of roentgen-rays in the study of the heart is directed toward the measurement of cardiac size. Heart size determination, comparable in accuracy to anthropological standards, is impossible even

under the most favorable conditions. A number of schemes have been proposed, however, whereby estimations of heart size may be derived from roentgen-ray measurements for comparison with computed normal values. These have met with varying degrees of favor in clinical practice. These methods group themselves into three general types: those which depend upon the value of one or more cardiac diameters, those based upon cardiac area measurement, and those which seek to express heart size in terms of volume. Measurements in terms of diameter have been in the past and are today more widely used in clinical practice than area and volume determinations which

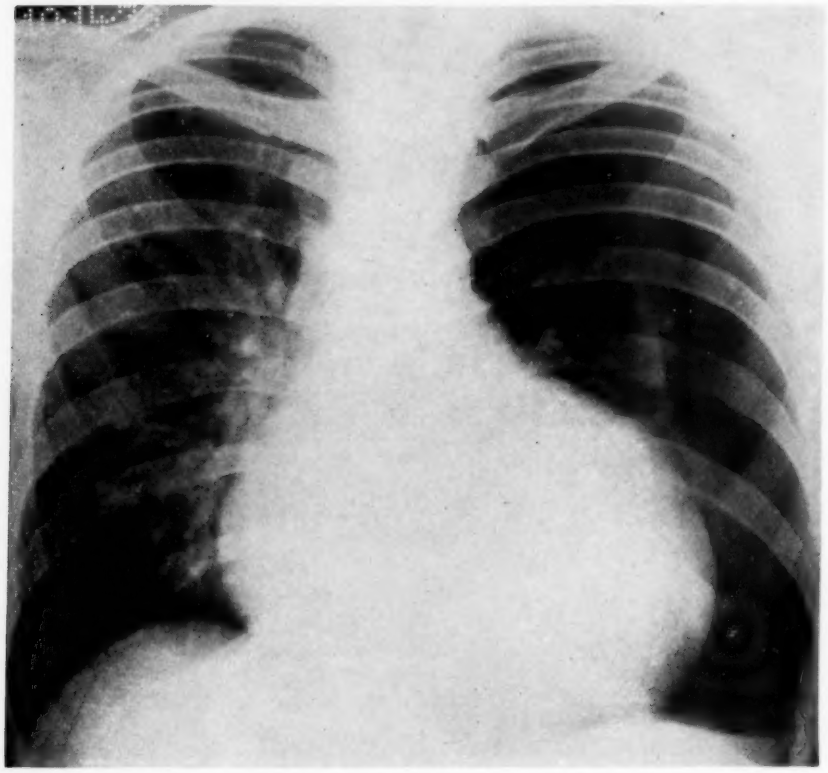


FIG. 4. Abnormal cardiac shape: pericardial effusion.

require somewhat more effort on the part of the examiner and, in some cases, highly particularized roentgenological study. If the heart were a regular and symmetrical solid, determination of one or more characteristic diameters or the area of certain sectional planes would serve perfectly well as a basis for computing volume. Since the heart is not a regular geometrical figure, measurements of this sort can be expected to yield only approximate values for volume. Direct measurement of silhouette area involves smaller inherent error than diameter measurement since deviations from regular spherical or ovoid curvature can be directly measured, at least

in those planes selected for area determination. The most direct method of volume determination as yet devised and proposed consists of reconstruction of the heart in plastic material by modeling the silhouette contours in successive stages of axial rotation. This can be done and as a matter of fact a modified, somewhat less awkward and less time consuming scheme is entirely practicable in those cases where highly accurate volume determination is sufficiently valuable to warrant the necessary effort.

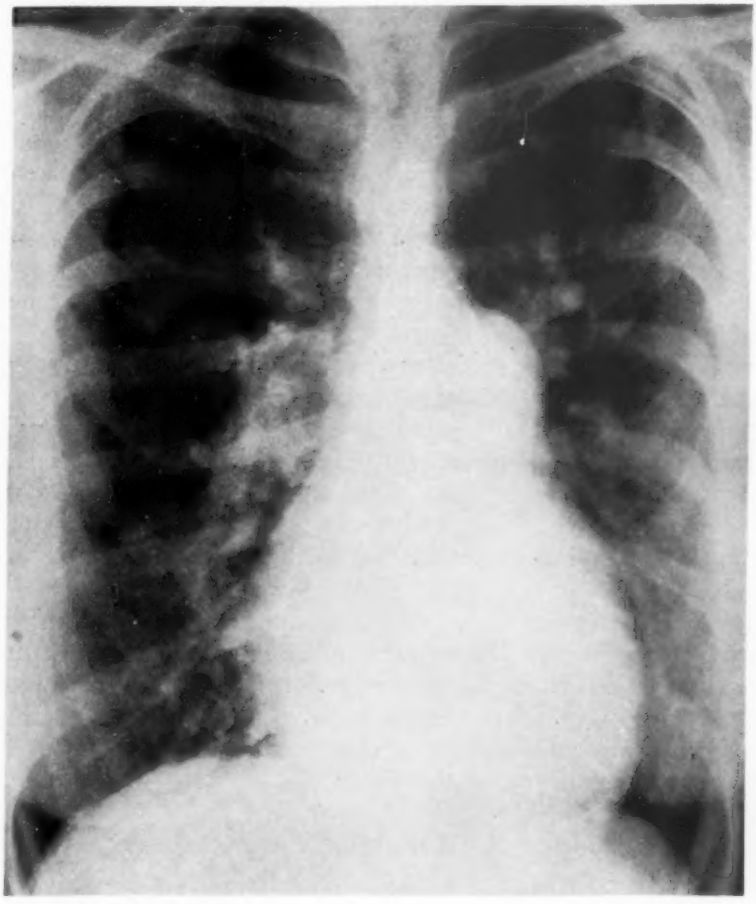


FIG. 5. Congenital heart disease: hypoplasia of aorta, patent foramen ovale.

Area measurements are obtainable with much less difficulty and a fair degree of accuracy by employing a draftsman's planimeter which expresses the silhouette perimeter in units of area. In some clinics a number of diameters are measured and reported as direct values or in the form of comparative indices with some other body measurement. The most commonly employed of these is the well-known Danzer ratio, which relates total trans-

verse diameter of the heart with total transverse diameter of the thorax. Actually this particular ratio is a relatively crude index of cardiac size which, if used, should be considered subject to wide limits of error.

Numerous variations of the three basic methods mentioned, as well as combinations of diameter and area measurements, have been proposed. The most extensive efforts to establish reliable normal values against which individual measurements may be compared are based upon frontal silhouette area and greatest transverse diameter determinations. Since area can be measured with reasonable accuracy, either by the employment of orthodiascopy or the measurement of corrected frontal plane silhouettes obtained radiographically, the adoption of this plan seems advisable.

Figure 6 shows the more commonly used cardiac diameters, the portion of a frontal plane cardiac silhouette ordinarily employed in area determination, and the manner in which an orthodiagraphic tracing can be similarly employed, as well as one plan of measurement based upon diameters obtainable only in the left anterior oblique projection. This diagram is taken from the record of a single patient and the values shown clearly indicate the variability to be expected when different methods of measurement are employed.

If one is willing to make necessary allowances for inherent errors known to exist in all methods of estimating cardiac size, numerical values may be very helpful in expressing various degrees of cardiac enlargement. It is often gratifying to be able to express progressive cardiac enlargement over a period of time in this fashion. The roentgenologist should constantly remind himself, as well as the physicians who refer cardiac patients to him for study, that numerical expressions of cardiac size are accurate only to a degree.

Figure 7, representing three interval examinations, shows very obvious progressive enlargement. Numerical expressions of heart size in terms of percentage variation from the expected normal as computed from age, height, and body weight, are very expressive of the changes recognizable roentgenographically and have the advantage of being easily transferred to the patient's case record in readable form.

Significance of Alteration of Cardiac Shape

No rigidly defined normal cardiac silhouette shape can be described in comparison with which all other shapes may be considered definitely pathological. This is true because in addition to individual variations comparable to those which occur in other parts of the body, the heart is readily affected in the matter of position and shape referable to body habitus as well as abnormalities affecting the vertebral column, the ribs and sternum, the lungs, the diaphragm and extra-cardiac structures which occupy the mediastinal space. Before ascribing any significant importance to apparent variations in shape, all of these possibilities must be carefully evaluated.

Cardiologists and roentgenologists, trained and experienced in such matters, are able with a reasonable degree of success to recognize, classify, and evaluate contour changes expressing anatomical alterations limited to or predominant in one or more chambers of the heart. Attempts on the part of

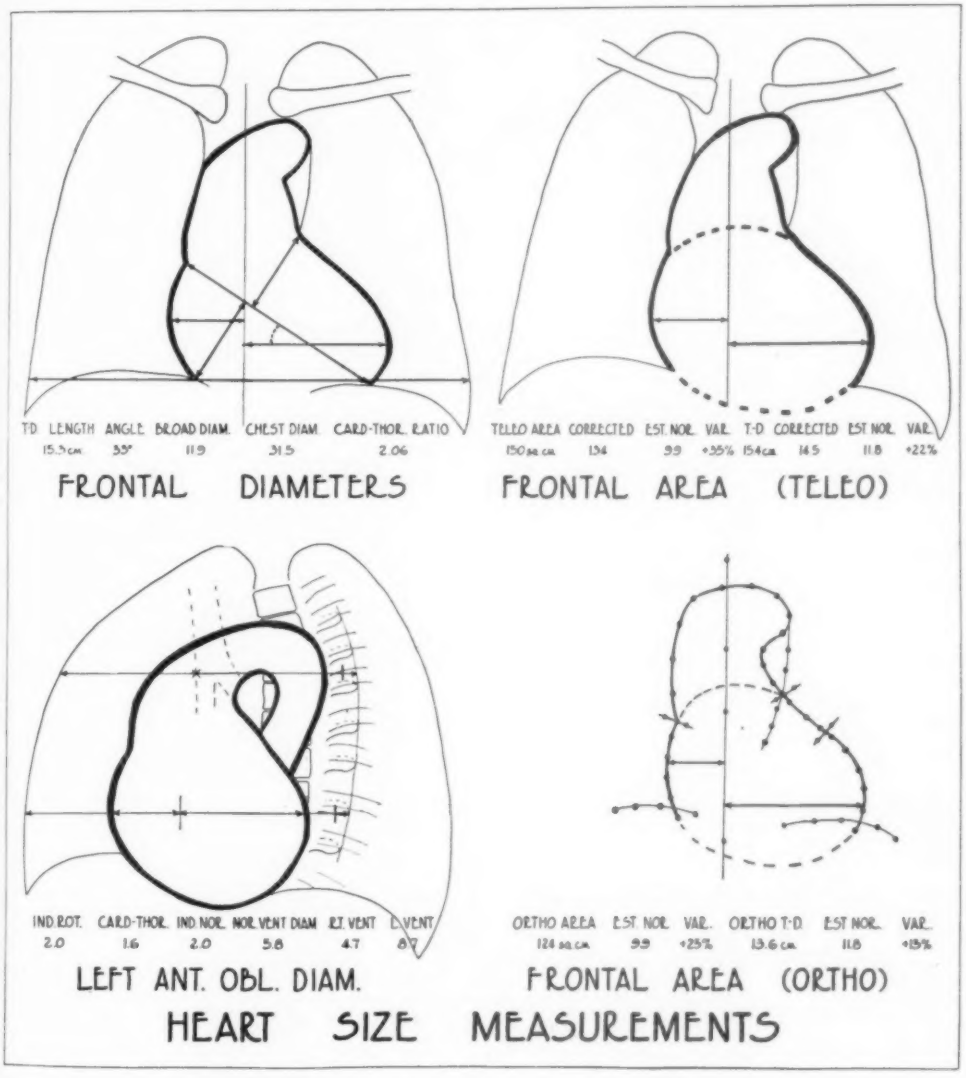

T-D LENGTH ANGLE BROAD DIAM. CHEST DIAM. CARD-THOR. RATIO
15.5 cm 35° 11.9 31.5 2.06
FRONTAL DIAMETERS
TELEO AREA CORRECTED EST. NOR. VAR. T-D CORRECTED EST NOR. VAR.
150 sq. cm 134 99 +35% 15.4 cm 14.5 11.8 +22%
FRONTAL AREA (TELEO)
IND. ROT. CARD-THOR. IND. NOR. NOR. VENT DIAM RT. VENT L. VENT.
2.0 1.6 2.0 5.8 4.7 6.7
LEFT ANT. OBL. DIAM.
ORTHO AREA EST. NOR. VAR. ORTHO T-D EST NOR. VAR.
124 sq. cm 99 +25% 13.6 cm 11.8 +15%
FRONTAL AREA (ORTHO)
HEART SIZE MEASUREMENTS

FIG. 6. Commonly employed diameter and area measurements.

unskilled observers to recognize the existence of various valvular lesions on the basis of such evidence are harmful since they create the false impression that changes in cardiac shape readily and accurately reflect specific valvular defects. Compared with evidences of cardiac enlargement, which should

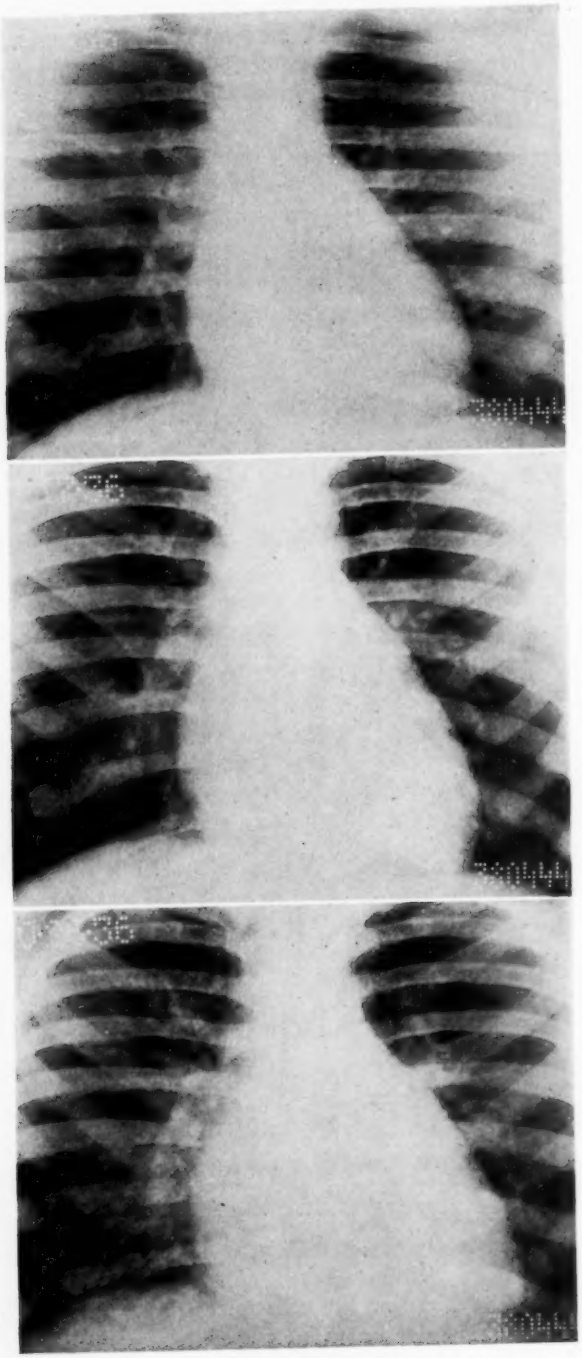


FIG. 7. Progressive enlargement of cardiac silhouette. + 12% + 32% + 49%

never occur in the absence of underlying disease, cardiac shape must be considered a far less reliable criterion of significant abnormality.

Certain variations in shape are more or less characteristic of some of the congenital anomalies involving the heart and great vessels. Considered from the point of view of the roentgenologist, the relatively accessible location of the left auricle, and the frequency with which changes in its size and shape are associated with narrowing of the mitral ring, render conditions in which stenosis of this particular valve is a feature, readily susceptible to identification by the roentgen method. Similar enlargement of the left ventricle associated with stenosis or insufficiency of the aortic valve, though recognizable in many instances, is far less uniformly detectable. In figure 8 are reproduced frontal and lateral roentgenograms showing unmistakable signs of left auricular enlargement. All other types of examination serve to confirm the diagnosis of well established mitral stenosis in this patient. The characteristic features are unusual prominence and sharp convexity along the upper portion of the left cardiac contour, the zone in which one would expect to find evidence of left auricular enlargement, and localized obliteration of the normally transparent retrocardiac space corresponding to the posterior location of this chamber. Enlargement of the heart shadow downward and to the left, without evidence of corresponding enlargement to the right of the mid line, or in the left auricular zone, bespeaks enlargement primarily limited to the left ventricle. Such findings are shown in figure 9. In this patient the diagnosis of aortic stenosis has been established clinically.

Roentgenological Signs of Pericardial Effusion

The presence of excessive amounts of fluid within the pericardial space offers many diagnostic difficulties for the roentgenologist, in spite of the fact that one might well expect this situation to lend itself remarkably well to his methods of study. In the early stages of the disease, pericarditis may be easily recognizable on the basis of suddenly developing friction rub without corresponding characteristic signs detectable roentgenologically. The heart may, of course, be enlarged and often is, but that is no reliable criterion of impending pericardial effusion. Once fluid develops, the most obvious effect is further enlargement of the cardiac silhouette. The density of the heart being almost exactly the same as that of normal and pathological body fluids, it is impossible to visualize the borders of the heart itself within the outlines of the distended pericardium. To a certain extent only may the presence of fluid be reliably detected by alterations in the contour of the heart shadow. These are not difficult to appreciate as a rule if the patient has been examined on repeated occasions. It is surprising, however, how often relative broadening at the base of the cardiac shadow and increased acuity of the angles formed by the diaphragm and the lateral borders of the heart fail to provide conclusive evidence even in well established cases of pericardial

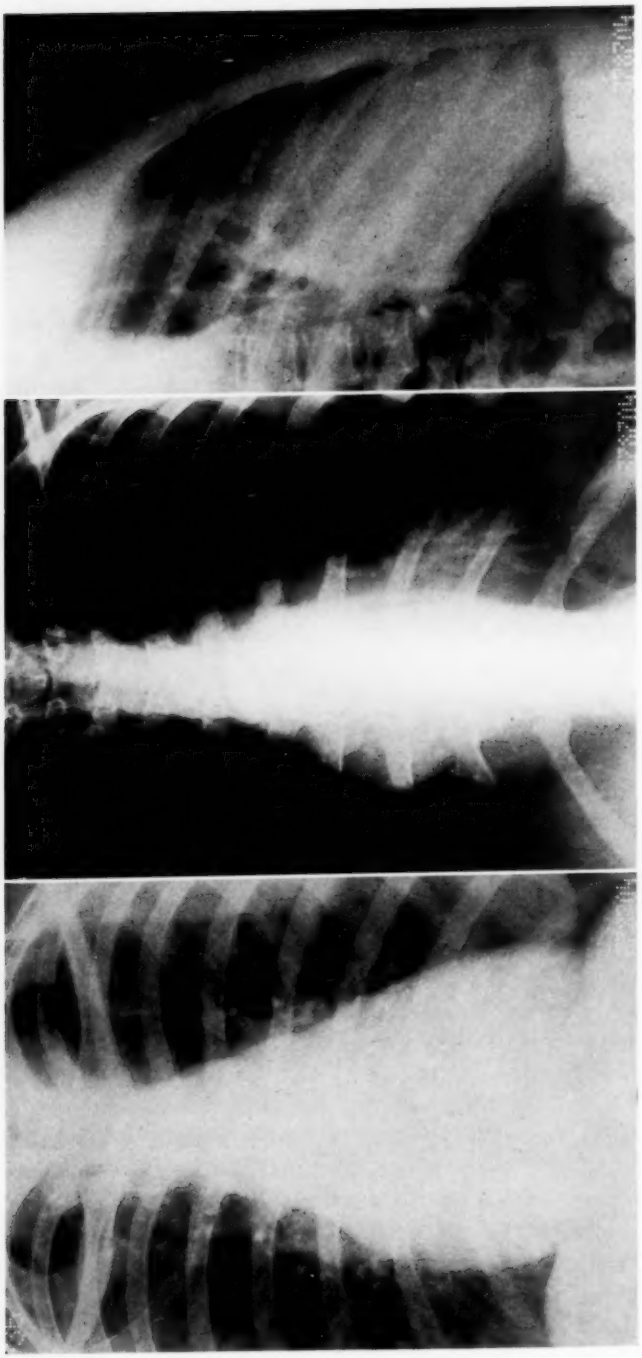


FIG. 8. Left auricular enlargement. Mitral stenosis.

effusion. By resorting to the use of the fluoroscope, one can recognize feeble pulsations of the shadow contours and examination of the patient, first in the upright, then in the horizontal position, will sometimes show suggestive or even characteristic alterations in the breadth of the cardiac shadow. Roentgen-ray examination may be very helpful as an adjunct to other methods of study, and may even on occasion be the first agency to discover signs suggesting this situation, but unrecognized instances of pericardial effusion, as well as occasions when this situation is erroneously reported, serve to emphasize the fallibility of roentgen signs in this disease.

FIG. 9. Predominant enlargement of the left ventricle.

When, because of the overwhelming clinical evidences of pericardial effusion, aspiration is carried out and followed by the injection of small amounts of air, cardiac roentgenograms are as a rule very startling in appearance. Reëxamination from time to time is a helpful means of determining the rate at which fluid is being re-formed, and sometimes the progressive development of intra-pericardial adhesions can be observed. Figure

10 is reproduced from films in a case of pyo-pericardium at the height of the disease and also after complete recovery following surgical drainage. Figure 11 illustrates the appearance which may be observed after fluid aspiration and the re-injection of air.

The Demonstration of Abnormal Opacities Within the Heart and Pericardium

The deposition of lime salt in the pericardium, the epicardium, and the loose connective tissues which surround the superficial coronary vessels constitutes an important contribution to the diagnosis of pericardial disease. When such depositions can be clearly demonstrated, even though the amount of calcium may be small, their presence constitutes proof positive of pre-existing inflammatory disease. When these deposits are massive, as is sometimes the case, roentgenographic findings are startling. To demonstrate such findings, lateral and oblique projections are the most desirable, although in the case of the smaller deposits the optimum angle of projection is best determined in advance fluoroscopically. Calcium deposits are seen to best advantage in roentgenograms prepared with the use of a Potter-Bucky diaphragm, or some other type of grid or lattice to enhance contrast. Figure 12 represents an example of extensive calcium deposition about coronary vessels associated with constrictive pericarditis in this particular instance.

Occasionally inspection of a chest roentgenogram will show single or clustered shadows of great density centrally placed within the cardiac silhouette, which represent lime salt deposition within the annulus fibrosus or within the leaflets of cardiac valves. Much more commonly such calcium deposits can be recognized fluoroscopically, although it is necessary to employ every available mechanical advantage in order to do so. With his eyes thoroughly accustomed to darkness, the operator must employ a very small beam of roentgen-rays of relatively high intensity, the most efficient fluoroscopic screen available, and no little ingenuity in the matter of advantageously rotating his patient in order to detect the presence of such shadows. Valve shadows, of course, are always projected within the contours of the heart, no matter what position is employed. When observed, calcified valves can be identified by their characteristic dancing motion. Aortic valve calcification in a case of aortic stenosis and regurgitation is shown in figure 13. The results of such observations have shown that the mitral valve is located somewhat more posteriorly and nearer to the cardiac apex than the aortic valve. Exceedingly rapid exposures are necessary to record correctly the shadows of valve calcification. Calcium deposition in either the annulus fibrosus or the valves themselves proves conclusively the existence of chronic inflammatory or degenerative disease.

Occasionally the roentgenologist is called upon to examine patients harboring opaque foreign bodies within the heart or in its immediate vicinity. Each situation of this sort offers its own problem and its own diagnostic

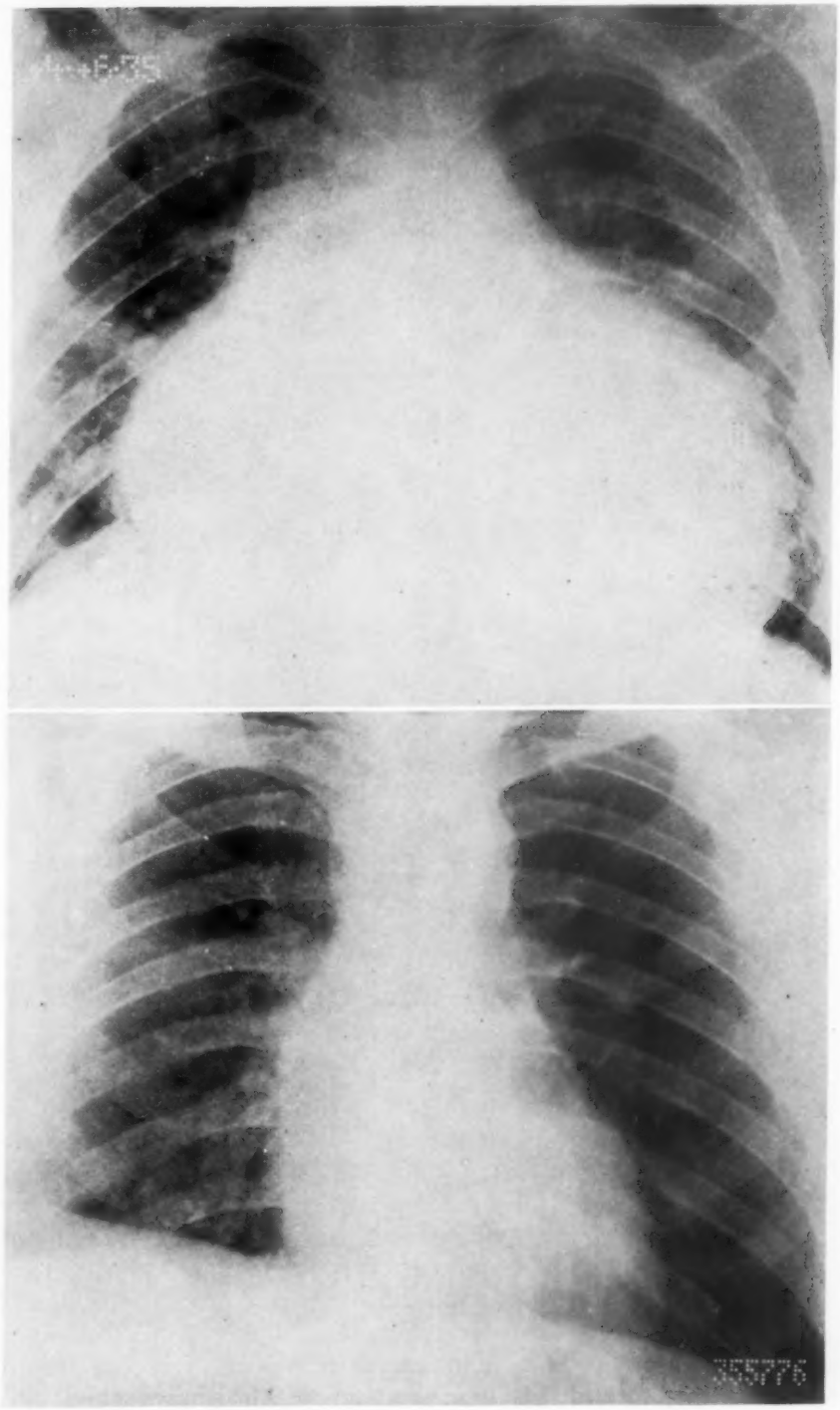


FIG. 10. Pyopericardium before and after surgical drainage.

reward. Occasionally metallic foreign bodies have been described within the chambers of the heart where they have been observed to reflect movements of the blood and the contractions of the cardiac wall. Sometimes fragments of bullets, broken knife blades, portions of aspiration needles, and other metallic fragments have been observed to lie within the pericardial cavity or actually imbedded within the muscle of the heart. It is obvious that if surgical removal of such objects is contemplated, preliminary localization with respect to cardiac landmarks is desirable and altogether feasible.

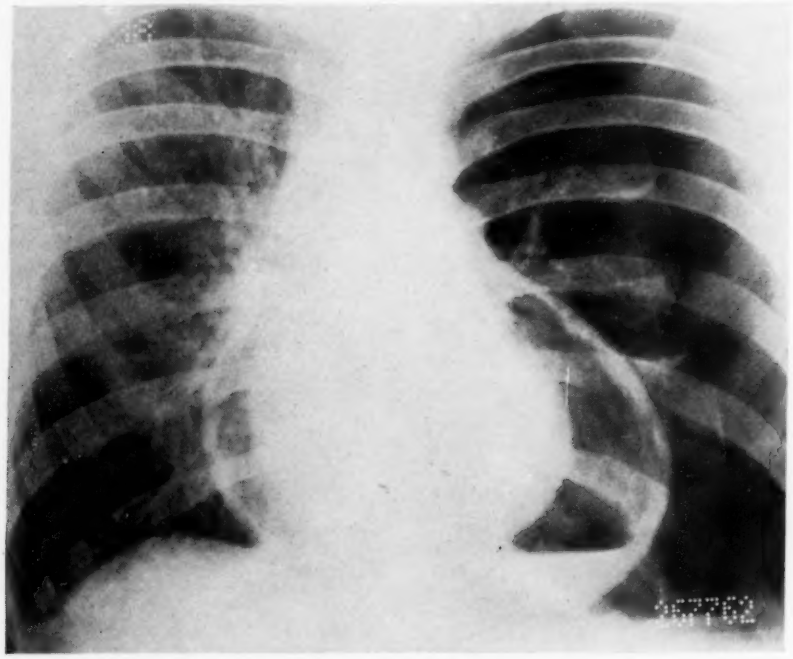


FIG. 11. Hydro-pneumopericardium.

THE STUDY OF CARDIAC MOVEMENTS

Movements of the cardiac borders can be studied with a considerable degree of accuracy by means of a number of modifications of the roentgenological method. Film may be moved at slow or fast speed behind a lead screen provided with a slit to record movements of a given point on the contour of the heart, thus providing a continuous record of the motion at this point throughout one or more cycles. If the motion applied to the film is of relatively short amplitude, a number of apertures can be arranged permitting the simultaneous study of the motion of the cardiac contour at a number of different points. Simultaneous recording of the electrocardiogram, venous and carotid pulse tracings, and amplified heart sounds give to

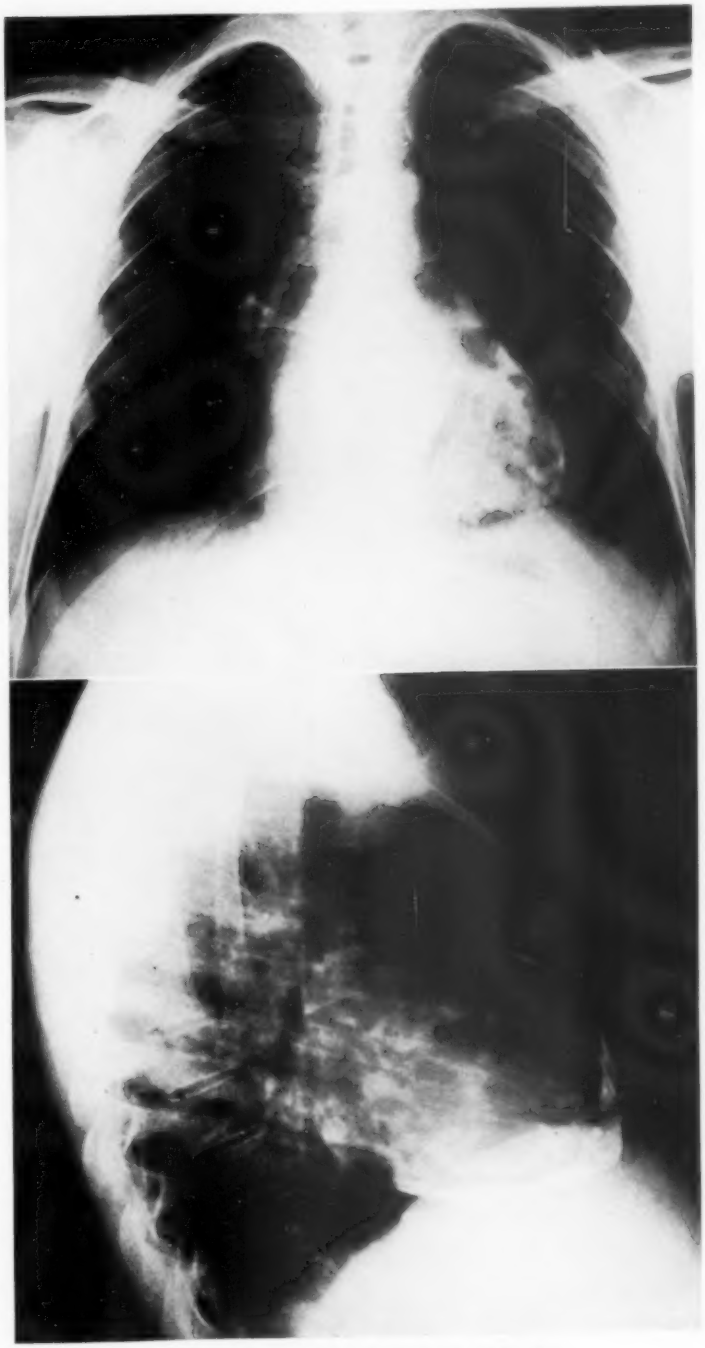


FIG. 12. Extensive pericardial calcification.

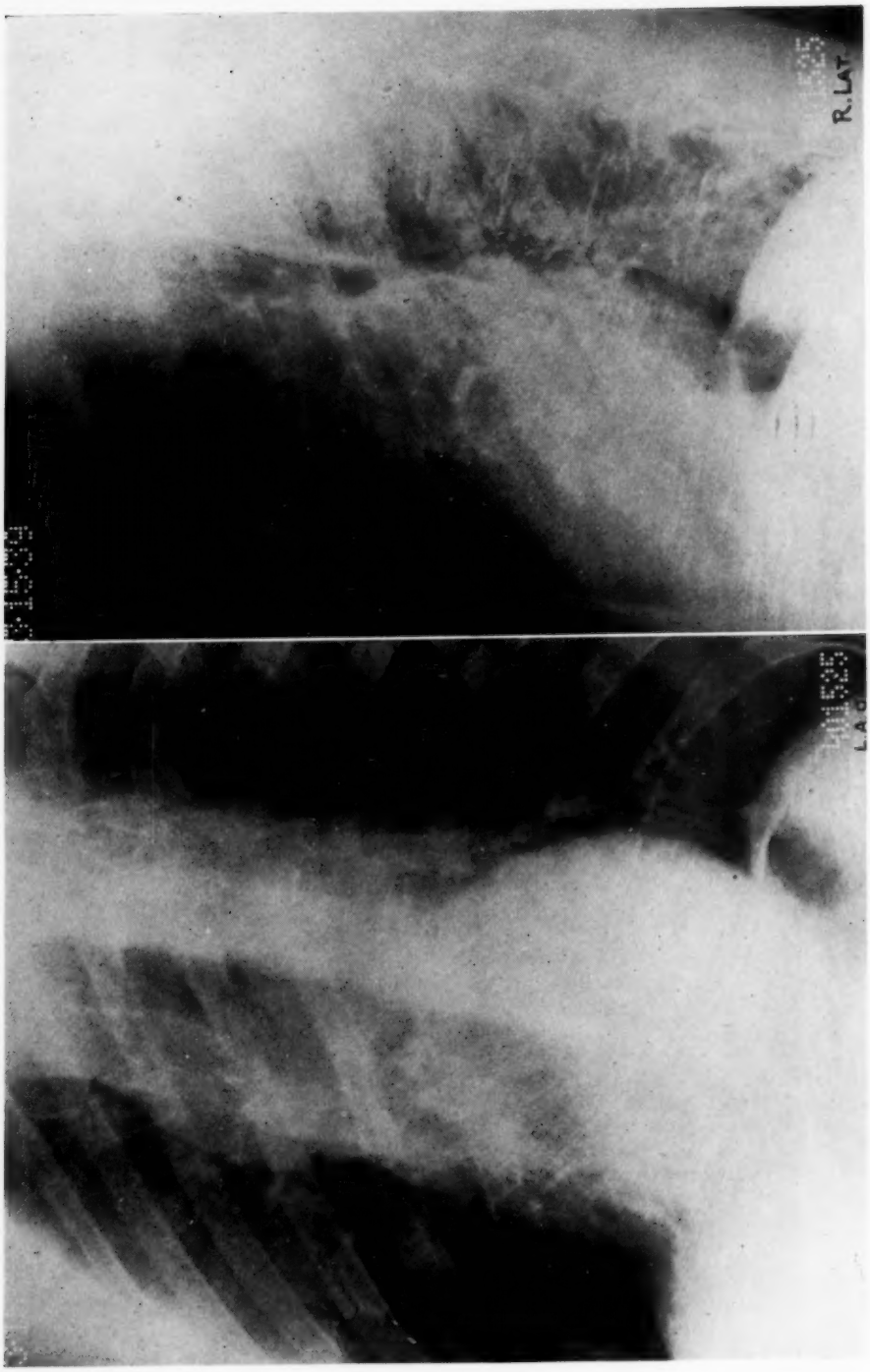


FIG. 13. Male, aged 33. Clinical signs of aortic regurgitation. Visible calcification in aortic valve leaflets.

the examiner a rich fund of accurate information regarding the behavior of the heart if intensive study of this sort is desired.

In actual clinical practice this method of study known as roentgen kymography is restricted for the most part to its employment for the purpose of identifying, on the basis of characteristic motion, certain segments of the cardiac contour in various projections which may for one reason or another appear to offer diagnostic possibilities. For example, one may want to know whether unusual prominence or fullness high on the left cardiac margin represents marked enlargement of the left auricle or bulging at the base of the left ventricle. As a rule this question can be answered quickly by simple fluoroscopic observation, but when the amplitude of pulsation is very short kymographic examination may be the only reliable means of making this determination. Direct comparison with a point of known identity quickly and positively identifies movement as auricular or ventricular in phase. The roentgen kymograph is also very serviceable in detecting and identifying the nature of pulsation in abnormal mediastinal masses. The recognition of non-pulsating segments along the ventricular contours is also rendered feasible and positive by this method of study.

Movements of the heart which are related to the phases of respiration can be observed quite readily on direct fluoroscopy and may be very enlightening in the interpretation of cardiac roentgenograms. On occasions movements of rotation and pulsation are transmitted from the heart to abnormal intrathoracic masses in such a manner as to greatly modify their roentgenological appearance. Sometimes such transmitted movements may very closely simulate intrinsic expansile pulsation even in the case of solid mediastinal and pulmonary tumors.

The Study of Blood Flow through Cardiac Chambers

If it were true that a distinct difference in density existed between heart muscle and blood under normal conditions, the physiology of cardiac circulation might be studied to excellent advantage by the employment of roentgenological methods of observation. Anatomical study of the chambers of the heart has been carried out rather commonly by the injection of opaque masses into the various chambers of the unopened heart in situ in the cadaver, and numerous experiments have been reported involving the introduction of various contrast substances into the blood stream as it enters the heart. Bubbles of air, droplets of iodized oil, and water soluble iodine compounds have from time to time been used. These materials have been introduced through needles placed in large peripheral veins, through catheters inserted through such veins to the entrance of the right auricle, and by way of cannulae passed into the left ventricle through the carotid artery. Because of their hazardous nature such experiments have been conducted for the most part upon animals. Somewhat similar procedures, employing contrast substances which can be administered intravenously with safety, are

used in the study of peripheral vessels. These have quite naturally whetted the appetite of practitioners and experimenters alike for a safe and practicable method of studying the flow of blood through the heart itself. Because of the rapidity of flow and the very rapid dilution to which injected contrast substances are immediately subjected, this problem is not simple in solution. Sizable quantities of very dense fluids are required. It does appear, however, that recent progress in this direction may well result in the development of a useful and feasible means of attacking the problem. Remarkable results in this field have recently been achieved by Robb and Steinberg.

Observations regarding the comparative size of the paired chambers of the heart, the presence or absence of septal defects, the presence and nature of other congenital malformations, the competence of valves, circulation time between various points within the chest, and other features of blood flow through the heart and its great vessels appear to be open for direct study. Perhaps the most promising field of study related to the use of contrast substances within the heart concerns itself with the possibility of identifying beyond question of doubt the vascular or non-vascular nature of obscure mediastinal masses. The frequency with which aneurysms, both pulmonary and aortic, masquerade as neoplasms or inflammatory masses is notorious and any reliable means of direct graphic differentiation will be warmly received.

Summary

Roentgen-rays may be employed in a number of ways in the study of heart disease. The extent to which such methods of study are employed depends in very large degree upon the ability, interest and experience of the observer as well as upon the apparatus and time at his disposal. Such examinations should always include fluoroscopy because intrinsic movements of the heart and changes in its position relative to respiration are so important. However searching roentgen examination may be, the objective findings by it made available are of little value until they have been carefully weighed in the light of other considerations by a competent cardiologist.

DEEP INJECTION OF NOVOCAINE FOR THE RELIEF OF PLEURAL PAIN *

By SIDNEY SCHNUR, M.D., *Houston, Texas*

PAIN is the most important and most frequent symptom in medicine.[1] To the physician it is of value in the diagnosis and localization of disease, but having served this purpose pain should be promptly relieved. When it interferes directly with a vital function such as respiration, relief is urgent. In this latter category is pain of pleural origin.

The treatment of the pleural pain of early pneumonia, pulmonary infarction, etc. has undergone few changes in recent years. In addition to counter-irritants, strapping and sedation with codeine or morphine, pneumothorax has been used recently in the more severe cases unrelieved by the other methods. Morphine has not met with universal favor because of its depressant action upon the respiratory center. Pneumothorax, although relieving pain, is a procedure whose value in pneumonia is still under investigation.

An attempt has been made to relieve severe pleural pain by local injection of novocaine into the pleura. The site of the maximum pain having been indicated by the patient one or more interspaces in this region were infiltrated with 5 to 10 c.c. of 2 per cent novocaine intracutaneously, subcutaneously and into the region of the pleura. Most of the novocaine was injected deeply. An ordinary hypodermic needle for the superficial infiltration and a No. 19 Wassermann type needle for the deep injection were used, care being taken to avoid the intercostal vessels by injecting at the upper border of the rib. Penetration of the parietal pleura may be recognized frequently by an accentuation of pleural pain or suddenly encountering resistance due to consolidated lung. Although it did not appear necessary to infiltrate between the two layers of pleura, piercing the parietal pleura (and presumably entering into the pleural cavity) seemed to give the best results.

Thirty-one cases of pneumococcus pneumonia, and one of pulmonary infarction suffering from severe pleural pain were used as subjects for this therapy. Each of these patients had typical sharp, lancinating pleural pain frequently associated with a grunt and aggravated by cough and inspiration. In most of the cases unsuccessful attempts had been made previously to relieve pain by the usual methods.

Pain. In each of the 31 cases of pneumonia, the sharp pleural pain disappeared immediately. In 25 there was complete relief, while six described a residual soreness. In the former group 18 had no recurrence of pain, while in the remaining seven it returned in five minutes, 10 minutes, 30 minutes, two hours, five hours, 12 hours, and 26 hours. Five of these were

* Received for publication July 9, 1938.

From the Department of Medicine, Long Island College of Medicine and Kings County Hospital, Brooklyn, New York.

easily controlled with narcotics or strapping and two were reinjected with partial relief. Of the six patients who complained of soreness after the original injection, three had recurrence of pleural pain in 15 minutes, 50 minutes and two hours. Reinjection aided one, while the other two required morphine for comfort. The case of pulmonary infarction responded immediately to novocaine, but the pain returned in 12 hours after which it could be controlled with codeine. In several patients used as control the pain was unaffected by deep insertion of a needle without injecting novocaine, and in three cases saline injection had little if any effect. In addition to the relief of pain, novocaine seemed to have indirect beneficial results.

Respiration. Each patient prior to the injection exhibited shallow, rapid respiration, the pleural pain obviously preventing full inspiration. Following the relief of pain, respiration was definitely altered; inspiration became deeper, the rate slowed, expiratory grunting ceased, and in several patients there appeared to be immediate improvement in the cyanosis.

Cough. A severe agonizing cough was common. The associated pain frequently prevented the patient from expectorating, thus causing occasional difficulties in typing. After pain was abolished, cough was no longer distressing and sputum could be obtained more easily. In the majority of patients after the injection of novocaine cough was less frequent.

Rest. Many patients studied in this series had not slept for 24 to 72 hours; they were restless and uncomfortable even after the administration of sedatives and hypnotics. The sudden change in some of these individuals after their pleural pain was relieved was striking. Many turned over and fell asleep within 10 minutes after the injection. There also appeared to be a corresponding improvement in the mental attitude.

Prognosis. The factors in the eventual outcome and the incidence of complications in any individual case of pneumonia are varied and numerous, depending on the age of the patient, time of onset of treatment, type of infection, use and amount of serum, alcoholism, etc. Since the cases studied were few and the above factors were uncontrolled, one cannot say at present how injection of novocaine affected the course of the disease. From the clinical point of view, it appeared to be beneficial. Other things being equal, since prognosis is partly dependent upon adequate rest and the relief of all distress and mental anxiety, and these are favorably affected by this therapy, one should expect a more favorable prognosis.

There were no immediate harmful effects from this therapy. Nor was there any apparent difference in the number of cases showing extension to other lobes, pleural effusions, empyemas or pneumothoraces compared to a group of approximately 50 patients in whom this method was not used. Bullowa [2] in a large series has shown that lung puncture in the diseased area does not carry an increased risk of empyema.

Discussion

The pleural pain of early pneumonia is one of the causative factors in the respiratory disturbance in the disease. The pain, by preventing inspiration, causes shallow breathing. The body response to this is tachypnea. The rapid shallow breathing which obviously causes imperfect alveolar ventilation of normal parts of the lung "is not only uneconomical but may actually increase anoxemia."[3] Meakins[4] states that rapid shallow breathing is one of the principal causes of the anoxemia occurring in pneumonia. Relieving pain which is partly responsible for starting this vicious train of events would seem therefore to be of importance.[5]

The sensory nerve supply of the pleura consists of a plexus arrangement of fibers in the parietal pleura.[6] These are branches of the intercostal nerves—one small area of pleura usually being supplied by several intercostal nerves. The pleura may be anesthetized by paravertebral, intercostal or pleural block depending on the distance of the nerve from the cord. Weiss[7] has occasionally obtained temporary relief of pain by intracutaneous infiltration. Paravertebral block is a surgical procedure. Intercostal block is said to be of value when the pleura is inaccessible to direct injection as in diaphragmatic and mediastinal pleurisy. Direct pleural injection is most valuable when small areas are involved as in early pneumonia because all the different fibers arising from a painful area are blocked at the origin necessitating fewer injections, and more important, the anesthesia seemed to last longer.

It is uncertain why a local anesthetic whose action is no longer than two to four hours should frequently abolish pleural pain permanently. In the natural course of pneumonia the pain is of relatively short duration, but it remains longer than four hours in most cases. Therefore the local anesthetic action alone cannot explain the permanent relief of pain. It is possible that the trauma of the injection or the irritating action of novocaine may after a short time cause a small localized effusion which separates the pleura, relieving pain. A localized traumatic pneumothorax due to the injection would probably have the same effect.[8] In several cases in which roentgen-rays were taken before and after injection, neither fluid nor air could be demonstrated in the pleural cavity. However, at least 150 c.c. must be present before it could be visualized by roentgen-ray, so that this explanation can not be excluded.

Summary

1. Novocaine was injected deeply into the painful area in 32 patients with severe pleural pain and resulted in immediate relief in every one. In 21 of these, pain was permanently abolished. In those individuals in whom pain recurred its severity was much decreased.

2. The beneficial secondary effect of this therapy on other symptoms in pneumonia, i.e. dyspnea, cough, restlessness, and mental state, is described.

I wish to thank Dr. J. Hamilton Crawford, Dr. Carl H. Greene, and Dr. Richard H. Bennett for the use of the cases of their services, in this study.

BIBLIOGRAPHY

1. MEAKINS, J. C.: Practice of medicine, 1936, p. 8, C. V. Mosby Co., St. Louis.
2. BULLOWA, J. G. M.: The management of the pneumonias, 1937, p. 107, Oxford.
3. MEANS, J. H.: Dyspnea, Medicine Monograph, 1924, v, 95.
4. MEAKINS, J. C.: Harmful effects of shallow breathing with special reference to pneumonia, Arch. Int. Med., 1920, xxv, 1.
5. HALDANE, J. S., MEAKINS, J. C., and PRIESTLY, J. G.: The effect of shallow breathing, Jr. Physiol., 1918, lii, 420, 433.
6. GRAHAM, E. A., SINGER, J. J., and BALLON, H. C.: Surgical diseases of the chest, p. 115, Lea and Febiger, Philadelphia, 1935.
7. WEISS, S., and DAVIS, D.: The significance of the afferent impulses from the skin in the mechanism of visceral pain, Am. Jr. Med. Sci., 1928, clxxvi, 517.
8. TCHERTKOFF, J. G.: Rôle of traumatism in induction of initial pneumothorax, Quart. Bull. Sea View Hosp., 1936, i, 398.
9. CAPPS, J. A.: An experimental and clinical study of pain in the pleura, pericardium and peritoneum, 1932, Macmillan Co., New York.

INITIAL MANAGEMENT OF TUBERCULOSIS WITH SPECIAL REFERENCE TO THE PSYCHOLOGY OF THE PATIENT *

By Lewis J. Moorman, M.D., F.A.C.P., *Oklahoma City, Oklahoma*

The initial management of pulmonary tuberculosis would be relatively simple were it not for the patient. Modern methods of diagnosis make it possible to observe, record, and evaluate the symptoms and signs of the disease. The nature and extent of anatomic changes may be accurately estimated and, by means of the roentgen-ray, visualized. With all the data available through the application of the usual diagnostic methods, the well informed physician should experience little difficulty in planning the most logical form of management. But, the effective execution of any program based upon symptoms and the purely physical and pathological conditions, must take into consideration the patient's personality, representing, as it does, the summation of all the hereditary and environmental influences of a lifetime.

The physician who thinks he has perfect control of a patient under his initial management, is probably not fully aware of the varied psychological possibilities. He fails to appreciate that herein are often explained some of the differences between animal and human clinical tuberculosis. Personality is constantly affected by the disease, and disease by the personality. If this were not true, the attending physician would be reasonably accurate in his estimate of the problems presented by the three clinical gradations of the disease.

In *minimal pulmonary tuberculosis* the initial management should consist of rest in bed with careful attention to hygienic and dietetic measures, preferably in a sanatorium, but possibly in a well-ordered home.

Moderately advanced. The initial management should be the same as the above, plus artificial pneumothorax or some other chosen form of collapse therapy. However, if all conditions are favorable and the indications for collapse therapy are not clear cut, such measures may be temporarily deferred with the hope of success through routine management. Institutional treatment of such a case is unquestionably preferable to home treatment.

Advanced. Initial management should definitely include sanatorium routine, plus necessary collapse therapy with close observation and careful diagnostic scrutiny for guidance in the probable successive steps of collapse therapy.

The above classification, with suggested management, is deceptively simple, for the constant advances in the diagnosis and management of tuberculosis place increasing responsibilities upon the attending physician. In

* Received for publication April 28, 1938.

doubtful cases he must see that all available diagnostic methods are employed. After the diagnosis is made he cannot well devise a therapeutic program until he has determined whether the case is minimal, moderately advanced, or advanced; whether it is acute or chronic; whether it is predominantly unilateral or bilateral. He must also recognize the presence or absence of cavities, and, if cavities are present, he must determine their size and location, the character of their walls, and the condition of the surrounding tissues. He must determine, if possible, the presence or absence of adhesions and the position and mobility of the diaphragm and the mediastinal structures. He must attempt at least a clinical estimate of the vital capacity of the lungs and he must appraise the cardiovascular system, with particular reference to the integrity of the heart muscle. He must recognize serious complications when present, as well as other associated pathological conditions. These demands require unusual knowledge of the anatomy and physiology of the intrathoracic organs, an appreciation of the pathology of the tubercle from early proliferation to cavity formation, special skill in physical diagnosis, and the wisdom of clinical experience. There must be a choice between home management and institutional management. In those chosen for institutional management, there must be a choice between routine management and surgical collapse. If the latter there must be a choice between artificial pneumothorax, intrapleural and extrapleural pneumolysis, phrenic-nerve interruption and thoracoplasty. Often there must be a decision with reference to simultaneous bilateral or successive bilateral pneumothorax, or a decision regarding cautious combinations of the various surgical procedures mentioned above. Obviously, in many cases, it is unfair to both physician and patient to leave the management of pulmonary tuberculosis wholly in the hands of the family physician. Even among specialists, the successful management of pulmonary tuberculosis demands consultation and team-work.

Thus far, we have briefly outlined initial management in the light of symptomatology and pathology. Unfortunately the disease and the patient are inseparable. Patient and personality are virtually synonymous, and personality finds expression through psychological response to environment.

Often the apparently well-poised patient upon being apprized of the presence of tuberculosis and the necessary therapeutic requirements, may, through the exercise of cultivated inhibitions, artfully conceal mild or moderate psychological conflicts. Nevertheless, these may initiate a physiological imbalance resulting in digestive disturbances, metabolic deficiencies, and a rise in the adrenalin and sugar content of the blood, causing inhibition of phagocytosis and a consequent lowered resistance to the progress of tuberculosis. These changes have been noted through clinical observation and confirmed by animal experimentation. The wise physician may anticipate such an eventuality and employ preventive psychotherapy, or, if he does not immediately sense the psychological difficulties and the patient is not exhibiting satisfactory response to management, he may be able successfully to

penetrate the veil of graceful acquiescence and discover existing occult psychological conflicts.

More emotional and less stable persons, upon being informed of the presence of tuberculosis, may immediately burst into tears and, if dramatically inclined, may fill the air with lamentations. In their misery, they often have genuinely sympathetic family confederates ready to magnify these psychological conflicts with uncompromising pertinacity. In many cases, this distressing complex may be promptly, or at least gradually, modified through education, which may replace exaggerated ideas with consoling facts artfully presented by a sympathetic, far-sighted physician.

Occasionally we find patients stricken with even more serious psychological conflicts, seeking the protection of silence. These individuals are in dire need of psychiatric help or even of psychoanalysis, and prompt measures should be directed toward a better understanding on their part of their physical condition, its therapeutic implications and probable prognostic possibilities. Well planned persistent efforts on the part of the attending physician with oft repeated conferences, may succeed in making a good soldier of a psychological weakling or a whimpering coward. Because of innate instability of the nervous system in certain cases, the obstacles may be insurmountable and the end hastened by continued anxiety and the consequent lowered resistance. Rarely in desperation, suicidal impulses may arise and surcease may be sought through self-destruction.

The patient's domestic and social situation is very important. For parents, the mental strain either of being in contact with their children or of leaving them behind is always a factor influenced favorably or unfavorably by the age, character, and temperament of the children, and by the environmental conditions, such as the adequacy and safety of home care, including all of the accustomed domestic amenities. Adoring mothers who cherish an abiding sense of sacrificial duty well performed, cannot surrender their position without psychological conflicts which may, in some cases, prove a serious handicap. Such difficulties may be overcome by convincing the mother that contact with children should be broken and management faithfully accepted in order that she may later safely resume her place in the home.

Separation of husband and wife, particularly in cases requiring sanatorium care, may occasionally lead to insurmountable psychological conflicts. Here the range and scope of evil possibilities hinge upon the character and temperament of the respective personalities and their ability to maintain equable social and moral standards under abnormal conditions. There is nothing so discouraging as domestic infelicity, especially when accompanied by the haunting fear of inconstancy. Not infrequently, an irresponsible personality with unstable psychological susceptibilities, may manifest serious conflicts because of wholly unwarranted fears. Such evil fears spring from a vivid imagination impregnated with the groundless illusions which so often follow physical inactivity. On the other hand, the attending physician occasionally finds an unsuspecting soul while "singing at her grinding,"

suddenly shocked by the deadening consciousness of a faithless spouse. Nothing leaves one so inert, so devoid of psychological response, so unfit for disciplined battle.

Unmarried lovers may suffer similar conflicts, often magnified by the fear that chronic invalidism may cool the ardor of a coveted suitor. Such fears may lead to the precipitate negotiation of matrimony with all the hazards of such an untimely union.

These problems of the heart place upon the attending physician varied responsibilities. Some may be successfully executed through the exercise of ordinary skill, while others may require more than the wisdom of Solomon. However, with openness of mind, the physician learns in the school of life daily lessons, and develops a certain skill in giving more than is demanded by strict measure. Through such giving, tolerance is broadened, perception is sharpened, and initiative finds its course. The exigencies of each case must suggest the method, which will necessarily depend upon the character of the metal, the heat of the forge, the weight of the hammer, and the desired result.

The resourceful physician, with sincerity of purpose and straightforwardness of action, may succeed in bridging gaping chasms and in healing sensitive wounds. As may be said of physical scars, psychological scars often memorialize heroic deeds. Such memorials should rest securely among the unheralded satisfactions of a doctor's life.

Obviously the wide range of psychological manifestations makes adequate discussion impossible. The attending physician must be ready to meet the needs of his tuberculous patients as they come from every stratum of society, psychologically geared to keep pace with this fast-going, highly scientific, mechanistic age in which mankind has seemingly turned from reliance upon religion toward the more tangible, yet in the end, less satisfying guidance of science and reason. When faced, however, with what they consider a serious life hazard, patients almost without exception, seem to suffer from an obvious sense of personal insufficiency and a need for an abiding faith in some unseen power or outside agency. Ibsen had this in mind when one of his characters, under emotional strain, is represented as saying: "Without a fixed point outside myself, I cannot exist!"

Even anti-Christian, self-sufficient Goethe, when threatened with destruction by storm on the rocks of Capri, quieted his terrified fellow passengers by urging them to pray and by reminding them of Christ walking on the water. The dangerous agitation of panic-stricken passengers brought prompt realization of their need of some anchor outside themselves. Though Goethe was then approaching forty years of age, his own mind swiftly reverted to childhood teachings for this stabilizing influence. After his priestly task was performed, he admitted "a certain sense of pleasure which seemed to derive from the Lake of Tiberias, for I could quite plainly see the picture from Marian's illustrated Bible hovering before my eyes."

Henry C. Link's book, "The Return to Religion," was inspired by a

recent exhaustive study of current psychology as influenced by the long financial depression. He feels that a return to religion offers the best solution and that the Bible remains one of the most promising texts for the solution of fundamental psychological conflicts. However, there are many avenues of approach and innumerable sources of help for the patient who is groping in the dark. A broad knowledge of literature, history, and biography will better enable the physician to interpret his patient's psychological needs and without being suspected of a designing interest to direct his reading along therapeutic lines. Often the most essential and helpful initial educational adventure is teaching the patient the plain truth about tuberculosis. The story in language he can understand is often a source of great comfort and seldom is it wholly discouraging. Rarely is a patient's condition so serious as to preclude the possibility of a ray of hope, based upon the application of acquired knowledge in the diagnosis and management of his own case. However, in many patients the truth should be given in graduated doses, never exceeding psychological tolerance.

The more nervous and fearful the patient, the more important the sanatorium becomes in the initial management. The daily contact with physicians, nurses, and other patients in a well ordered sanatorium life usually serves as a revelation, inspires confidence, increases knowledge, and dissipates fear, thereby creating the best possible conditions for progressive improvement. For many there is nothing more hopeless than to lie down at home with the shocking consciousness of the intimate presence of a dread disease, fully aware of the partially concealed anxiety of poorly informed yet sympathetic loved ones, obviously ignorant of the patient's most urgent needs. Genuine poverty and the necessary household penury often serve as aggravating factors. Such an environment encourages dangerous introversion and may cause the patient silently to hug his own burden of bitterness through long days and nights, tortured with a hopeless sense of fear and uncertainty and possibly harboring the spirit of rebellion so common in the course of a great catastrophe.

The attending physician must ever keep in mind the fact that mental adaptability is limited by individual characteristics and that psychological adjustments, though difficult, must be made a part of every initial therapeutic program in order that valuable time may not be lost. It is difficult to pursue an effective educational program in the home, yet it is not impossible. Through the patient application of the attending physician or the well-trained public health nurse, the acquisition of knowledge and understanding may replace doubt, fear and rebellion, with hope and its attendant virtues.

The psychological appraisal of the patient and the educational program should have their inception when the patient first enters the physician's presence. The latter's success will depend upon his own knowledge of human nature and what Oliver Wendell Holmes called "intuitive sagacity." From the moment of first contact with the patient, the wise physician will be gathering information which will serve as a guide in making plans for his

initial management. By the time his diagnostic studies have been completed he will have, at least partially, determined the psychological trends and his conclusions will materially aid in the choice between home and sanatorium management and the determination of educational requirements.

The education of the patient is definitely a part of the physician's responsibility and should be wholly in his hands or under his direction. It is well to remember there is no short cut, no swift approach, no possibility of sudden arrival. It requires infinite patience, well-poised perseverance, adequate resources, and genuine spontaneity, with generous lessons which never exceed well guarded reserves. It should be designed to meet each patient's needs and should support the attending physician's method of management. As a part of initial management, this becomes invaluable to both physician and patient. If education is not properly supervised, the patient may discover conflicting opinions as to practices and procedures and may be tempted to depart from his physician's instructions. This disturbs confidence, interrupts therapeutic routine, and may create unfavorable psychological conflicts.

Physicians, nurses, and social service workers must constantly guard against thoughtless remarks which may be misconstrued. A misplaced word may prove serious. A passing remark by a friend or another patient may result in a wakeful night or a week of useless anxiety. The educational program and the daily routine should be designed to prevent or to meet such psychological events. The physician on regular rounds immediately observes obvious conflicts and if the need arises makes an effort to discover concealed fears and worries.

It is not uncommon to find the patient secretly worried about new symptoms or signs, or the aggravation of old ones. It may be shown that such worries are unwarranted or even when justified by pathological changes, the mental conflict may be corrected by a careful explanation, especially if there is a reasonable hope of prompt improvement. Otherwise, such conflicts may go on indefinitely. John Keats was driven to Italy by a streak of blood; Shelley was similarly impelled by persistent symptoms and signs; Robert Louis Stevenson finally staked his last dollar on a seventy ton schooner because of unabated toxemia, and unresolved psychological conflicts.

Early in the course of treatment the patient should be impressed with the fact that both mind and body must be wholly committed to the task of getting well and that there is no respite. Through proper education, he must be directed into avenues of self-expression and the execution of enlightened responsibility. Finally, every patient must learn with Carlyle that the duty of being brave is an everlasting duty, even though it may lead to the last great mystery.

This discussion of psychology must not end without calling attention to the fact that the success of initial management may depend largely upon the patient's estimate of the attending physician. We must not forget that while we are examining patients, patients are examining us. Of all the

patients who have spoken, none is more worthy of a hearing than Henri Frederic Amiel:

"Why do doctors so often make mistakes? Because they are not sufficiently individual in their diagnoses or their treatment. They class a sick man under some given department of their nosology, whereas every invalid is really a special case, a unique example. How is it possible that so coarse a method of sifting should produce judicious therapeutics? Every illness is a factor simple or complex, which is multiplied by a second factor, invariably complex . . . the individual, that is to say, who is suffering from it, so that the result is a special problem, demanding a special solution, the more so the greater the remoteness of the patient from childhood or from country life."

"The principal grievance which I have against the doctors is that they neglect the real problem, which is to seize the unity of the individual who claims their care. Their methods of investigation are far too elementary; a doctor who does not read you to the bottom is ignorant of essentials. To me the ideal doctor would be a man endowed with profound knowledge of life and of the soul, intuitively divining any suffering or disorder of whatever kind, and restoring peace by his mere presence. Such a doctor is possible, but the greater number of them lack the higher and inner life, they know nothing of the transcendent laboratories of nature; they seem to me superficial, profane, strangers to divine things, destitute of intuition and sympathy."

THE LIMITATIONS OF GOVERNMENT IN MEDICINE; THE SAN FRANCISCO EXPERIENCE*

By J. C. Geiger, M.D., F.A.C.P., A. E. Larsen, M.D., and J. P. Gray, M.D., *San Francisco, California*

Introduction

Recent months, more than ever before, have seen the development of concentrated interest in and extensive discussion of the problems of medical care, particularly as to governmental participation in their solution. The mere fact that representatives of the various groups interested in the problem, from all sections of the country, have met in important conferences of national scope to discuss all aspects (medical, economic, sociologic and administrative) in itself demonstrates progress.

American medicine today leads the world—scientifically and in all its humane aspects. Much of the discussion is built around public health and the lack of medical care. Public health, as such, is really not the duty of organized medicine. It is the duty of government, whether it be city, state, or national. Therefore, if there has been any neglect of public health in any locality, the blame should be placed where it belongs—on government. Certainly in San Francisco organized medicine has always supported the Department of Public Health. The politician (at least in the past) has not seen the vote-obtaining possibilities in humanitarian activities of government, such as public health. The fact remains that many of these activities originate from physicians, nurses and medical social workers and not from the government, though the latter is usually quick to absorb them. There must be realized, too, the critical and often adverse reaction of tax payers to accelerated budgets for such activities.

Adequate medical care in all its ramifications (which would include clinics, dispensaries, hospitals, and the necessary laboratory tests and home visits) should be divided into three groups: (1) those who cannot pay because of a disproportion between income and their medical needs; (2) those who should pay but find themselves in great difficulty because of their own budget limitations and ineptness in planning for illness; and (3) the smaller group who can pay for anything at any time.

Experience with the first group is available in San Francisco. With the second group, there is no doubt that medical opinion has been divided, but that division is more apparent than real. The division is in two schools: (1) compulsory health insurance, which many feel very definitely that these United States should never adopt in spite of the many good and acceptable features in several European countries; (2) voluntary health insurance

* Read at the New Orleans meeting of the American College of Physicians March 27, 1939.

which a large portion of the medical profession thinks should be the American system and whereby the patient may have, at a reasonable cost (not yet absolutely determined), choice of hospital and choice of physician. The dentist and the nurse, especially in home care visits, are seldom, if ever at all, mentioned in such a scheme, and yet the nurse is indispensable for the care of the ill, as is likewise the dentist in a great variety of diseases. Moreover, the seeming neglect of postgraduate training for the physician is an oft-repeated challenge not yet entirely answered by organized medicine or the medical colleges.

In the San Francisco set-up the limitations of government in medicine are thought consistent and there is no medical or public health neglect within the budget allowed. Moreover, the Department of Health lives in peaceful existence with organized medicine. If the program of public health should include hospitalization and home care of the indigent (classified as such because of their medical needs and limited earning capacity), which has not been the case heretofore, then again the matter is for government through health departments, and not through organized medicine. It is the rule rather than the exception that physicians give of their time, skill, and energy, without compensation. Even if this problem could be solved and properly budgeted to include the physicians, there still would remain the care of the moderate income group. It is this group that becomes the pièce de résistance for argumentative health insurance advocates.

For the reason that the experience in San Francisco has been rather widely recognized as having certain unusual aspects, it is believed appropriate that these be described in some detail so that the experience in this one metropolitan area may be available to others, not because the San Francisco experience is in any sense set forth as the ideal, but rather that attention may be invited to the limitations of the system as well as to the progress that has been made in this one community over a period of years.

San Francisco, a cosmopolitan population group of approximately 690,000, occupies an area of less than 50 square miles of hilly terrain at the tip of a peninsula, surrounded on three sides by waters of the Pacific Ocean and San Francisco Bay. With the facilities of one of the world's finest harbors available on its waterfront, San Francisco has developed into one of the largest American ports, and has been referred to, aptly, as the gateway to the Pacific. The metropolis is recognized as the commercial, transportation, and financial center of the Pacific Coast. Of interest also, in the presentation of the subject of this paper, is the fact that the community has a city and county form of government under a freeholders' charter, with noteworthy stability of administration.

From the medical point of view, San Francisco has many advantages as well. It is the medical center of the Pacific Coast, being the seat of two outstanding medical schools (the University of California and the Leland Stanford Junior University); three great hospitals operated by the Federal Government (the Letterman General Hospital of the United States Army, the

Marine Hospital of the United States Public Health Service, and the Diagnostic Facility of the United States Veterans' Administration); the nationally recognized San Francisco Department of Public Health, which includes the San Francisco Hospital; extensive hospital and outpatient services in non-official or voluntary hospitals of high standard, and, for the dependent portion of the population, a medical care program providing both inpatient and outpatient services that has attracted the attention and favorable impression of prominent students of public welfare and public health.

The integration of these various facilities into the whole community plan is not complete, but progress toward this objective, it is believed, merits description.

The Official Services

Official agencies in the medical care program in San Francisco are two departments in local government (the City and County of San Francisco), the Department of Public Health and the Public Welfare Department, and one branch of the State government, the State Relief Administration in San Francisco.

The Department of Public Health

Among health departments of major cities of the United States, the San Francisco organization has the same unique status of including the institutions maintained by the municipality for the care of the indigent sick, infirm and aged. Of no little import in the maintenance of balance between preventive or orthodox public health services and curative or institutional services, is the fact that the direction of the Department has been and is placed in the hands of a public health administrator rather than a hospital administrator.

The Department is set up in three sections, all of which participate in the program: the technical section (non-institutional and non-medical services, including vital statistics, laboratories and the inspectional bureaus; the medical-dental-nursing section (non-institutional medical services, as communicable disease control, child health services, public health nursing); and the institutional section (the San Francisco Hospital, the Laguna Honda Home, the Hassler Health Home and the Emergency Hospital Service). More closely allied to the institutional section administratively, but also very closely related to the medical-dental-nursing section, are the chest diagnostic centers, the outpatient obstetrical service, the venereal disease diagnostic and treatment centers and the city physicians, treating persons in their homes.

The technical section activities, although non-institutional and non-medical, provide services of importance to the public health of San Francisco, particularly in food and milk control, laboratory service, industrial hygiene and plumbing inspection. But of more specific interest to the subject of this paper are two other services: vital statistics and housing inspection.

Vital statistics, in the San Francisco Department of Public Health, has been extended beyond the study of mortality, natality and morbidity, in the ordinary sense, to include the study of statistical data from all sections of the department, including other technical services and the institutional services. This richest source of information serves the Director of Public Health, the Department, and the community in presenting data pertinent to the problems of public health and medical care.

Housing, as a factor in public health and public welfare, is recognized today as highly important. Although the extent of the sub-standard housing problem in San Francisco is perhaps not as great as it is in many of the older centers of population in the eastern part of the country, the problem does exist to considerable degree. For more than 20 years the State Housing Act has been an effective legislative instrument permitting improvement in housing in San Francisco and other cities of California. The Housing Inspection Division of the Department of Public Health has been responsible for the abatement of many nuisances, the demolition of large numbers of unsafe, unsanitary and unhygienic buildings used for dwelling places, with the result that the under-privileged persons living in such surroundings and under such conditions have had to live in other quarters which were at least less hazardous to health and happiness.

Partly, as a result of this type of work, there has been organized by ordinance the San Francisco Housing Authority which, through Federal subsidy, has been allocated funds of at least $15,000,000. If a health department decides in its wisdom to destroy tenements that are unfit for human dwellings, then it is equally logical to demand dwellings for replacement. It remains to be seen how effective the efforts of the San Francisco Housing Authority will be in supplying suitable buildings for this low income group.

The services within the medical-dental-nursing section, obviously, are directly related to the preservation of the public health. In the Bureau of Child Hygiene, all child health services are brought together in the administration of district health centers, well-baby conferences, school medical and nursing services, dental services, prenatal and postnatal supervision, nutritional work and the care of physically handicapped children. Public Health nursing, administered as a division within the Bureau of Child Hygiene, permeates the entire field of child health and, indeed, it is in this group of activities particularly that there is demonstration of the truth of the dictum, "the public health nurse is the wheel-horse of the public health organization."

As in several other cities, the district health plan takes the services of the health department to the neighborhood. The well-baby center is open to all children, without respect to socio-economic status, as an educational function. No treatment is provided for the sick child; in such instances referral is made to the family's physician or to a clinic if the family is unable to pay a physician. Dental care, for children up through the tenth year, is provided for those whose parents cannot afford the services of a

privately practicing dentist, the care consisting of prophylaxis, extractions and fillings. No orthodontia or prosthetic work is attempted in the service, since the facilities and personnel do not permit the long term, highly specialized and individualized care that such a program would require. A minimum amount of funds is available, however, for this type of dental care, but the needs far exceed this amount.

School medical and nursing services include medical inspection of school children, with special diagnostic problems studied in a well-equipped diagnostic center (electrocardiography, roentgenology, fluoroscopy, ophthalmoscopy, etc.), including audiometer testing and close working relationships with sight conservation classes, health schools and similar special facilities. There are in all two health schools, seven health classes, five sight saving classes, one school for the deaf, two contact classes for the hard of hearing, and the Sunshine School for crippled children.

All medical and nursing services in the public schools, parochial schools and junior college are coördinated under the Director of the Bureau of Child Hygiene within the Department of Public Health. The medical examination of school children by the family's own medical attendant is encouraged, and, under an arrangement worked out between the Department and the San Francisco County Medical Society, these examinations are reported by the physician to the Health Department on forms supplied and distributed through the Schools. Immunization against diphtheria and smallpox are not offered in the schools until three months after the physician has been requested to do so in connection with his examination of the child. The correction of remediable defects has been encouraged as a function of the physician, too, rather than of the public service, if the parents can provide the care. The supplying of glasses is through public funds which are totally inadequate. The success of the plan, which has been in effect in San Francisco over a period of three decades or more, lies in the interrelation between the Department of Education and the Department of Public Health. The Director of the child health services serves as the liaison officer between the Director of Public Health and the Superintendent of Schools, so that there is every opportunity for clearance of problems through an established channel.

Prenatal and postnatal instruction and guidance are provided by public health nurses and physicians working with patients registered in the outpatient obstetrical service. Group instruction is given in the center, and individual instruction in the home. The service is available to any pregnant woman having legal residence in San Francisco, if she is unable to provide medical care for herself, or if her physician requests such instruction. The patient is seen by the physicians of the outpatient obstetrical service at regular intervals during pregnancy, and concurrently the nurses make home visits. With the onset of labor, multiparous women are cared for at home if conditions therein are suitable and no complications of labor are manifest; and primiparous women are taken into the San Francisco

Hospital's obstetrical service. After the post-partum period, the public health nurse continues to guide the mother through return visits to the outpatient obstetrical center for follow-up of the mother's condition and visits to the well-baby center for diet supervision and habit-training for the baby. For the very low maternal and infant mortality rates in the group served by these two services, even lower than the notably low rates that obtain for the city as a whole, San Francisco can well be proud.

Nutritional work, particularly with children of school age, has been done only to a limited extent. Dental hygienists in the dental unit of the child health services carry out a rather intensive health education program, working with a supervisory public health nurse. Studies have been made by physicians and nurses in the Bureau of the nutritional status of children in the schools, with comparisons drawn between those not receiving relief and those receiving relief, in the days when "relief in kind" was given. Perhaps at this time the fact is worthy of note that this study showed that a better state of nutrition was found in the group from families receiving relief than that found in the "control" group, that is, from families not receiving relief. For the underprivileged school children milk is furnished in the school cafeteria at public expense, those receiving milk being selected by the principal of the school. Complete hot meals are provided those handicapped children attending the two special health schools.

For over 20 years California has had a state law providing care for crippled children. Since in San Francisco the official public health agency has all the facilities for the care of such handicapped children, the entire problem, from special care in schools to highly specialized orthopedic care in the San Francisco Hospital, is coördinated in the child health services. Finally, children who are wards of the Juvenile Court are supervised medically by physicians from the Department of Public Health, each child receiving a complete physical examination and having appropriate care and treatment outlined and arranged for him.

Facilities for the diagnosis and treatment of venereal disease, heretofore handled on a coöperative basis with the Outpatient Departments of the two University Hospitals, were recently developed more fully as a function of the Department of Public Health with the support of the State Department of Public Health. With aid from federal sources (United States Health Service under the Social Security Act) through the State Department of Public Health, additional clinic facilities have been secured and the epidemiologic aspects of syphilis and gonococcus infection likewise are being developed to a level comparable with the epidemiologic studies made of the other communicable diseases.

Chest diagnostic centers are maintained by the Department in conjunction with the outpatient clinics of the two University Hospitals, in one voluntary hospital and the San Francisco Hospital. Any physician may refer his patients to these centers for study, examination, tuberculin testing and roentgenologic investigation. Adolescent school children are given

tuberculin tests and roentgen-ray follow-up of all reactors is arranged through the school diagnostic center, all within the child health services. If hospital care is indicated, the chest diagnostic centers and the school diagnostic center feed into the San Francisco Hospital through the social service of that institution.

The institutional services of the Department include: the San Francisco Hospital, a general hospital of about 650 beds, 500 beds for the care of the tuberculous, 120 beds for the care of those affected by other communicable diseases; separate maternity and psychopathic units of 130 and 88 beds respectively; the Laguna Honda Home of 2,000 beds, which is the relief home for the aged and infirm who need institutional and custodial care; the Hassler Health Home of 110 beds for the care of tuberculous of good prognosis; and the Emergency Hospital Service comprising six stations and ambulance service for emergency first-aid treatment at all hours.

A recent bond issue of $1,600,000, supplemented by P. W. A. funds of $1,000,000, will allow the Department of Public Health to expand its hospital facilities to include the modernization of the San Francisco Hospital, additional facilities at the Hassler Health Home for the chronic tuberculous, and, perhaps, the convalescent, and an additional medical hospital building for the Laguna Honda Home for the care of the chronic patients.

The San Francisco Hospital, giving inpatient care to approximately 13,500 patients yearly, is used as a teaching hospital by both the University of California Medical School and the Stanford University School of Medicine. The scope of the work done, as well as the quality of the service rendered the indigent sick of San Francisco, is unsurpassed on the Pacific Coast. Testimony to the attitude of the community toward the institution which it maintains for its indigent sick is found in the fact that budgetary needs have been met with consistency by increases from year to year, even through these last several years of stress. The advantages to the two medical schools have been great, obviously, but the City and County of San Francisco have been the recipients of service from some of the greatest medical minds of the West as regularly visiting members of the staff. This hospital is guided by an executive staff selected from the faculties of the medical schools of the universities, and members having the rank of professor. The remainder come from the staff of the Department of Public Health. There are included special committees on therapeutics, pneumonia, acute anterior poliomyelitis, laboratory practices and emergency hospital procedures.

Admissions to the San Francisco Hospital and other institutions of the Department are handled through the social service department. Of more than 27,000 applicants yearly, approximately half are found eligible on the basis of standards of residence, indigency and need for hospitalization. The San Francisco Hospital is maintained for those residents of San Francisco who are in need of hospital care and unable to provide it for them-

selves. The person able to pay his physician and a hospital, on a full or part-pay basis, is not accepted for care.

There is no part-pay plan in effect. If a patient is admitted in an emergency under circumstances precluding investigation, he is removed to another hospital as soon as his condition permits and he is billed for his treatment at rates set annually by the Board of Supervisors. For obvious reasons, the standards for admission are somewhat less rigid for tuberculous persons, for others whose illnesses are of similar chronic type requiring long-term care and for those affected by acute communicable diseases for which facilities are not available in other hospitals. Standards of eligibility are maintained by the social service, with certain flexibilities as indicated above left to the discretion of the Director of Public Health, but it is to be emphasized that the institutions of the Department are maintained for the indigent and medically indigent, and under no circumstances is the hospital in competition with privately operated, endowed, or other non-official institutions.

It is believed appropriate at this point to emphasize the fact that, while certain limited outpatient services are provided in some of the units already presented (outpatient obstetrical service, chest diagnostic centers and venereal disease diagnostic center, and, in a remote sense perhaps in the well-baby centers, school diagnostic center and dental centers), the City and County of San Francisco does not maintain a true outpatient clinic. To facilitate the subsequent observation of persons treated in the hospital, there is maintained a follow-up clinic, to which persons discharged from the hospital return for study and observation over longer or shorter periods. The Emergency Hospital Service does not provide care on a revisiting basis, referring patients treated therein to their own physicians or to clinics. For many years the general attitude of all concerned has been that the interests of the community might be served best if the outpatient clinics and dispensaries maintained by and in connection with the universities and various voluntary or non-official hospitals supported in part by the Community Chest of San Francisco were utilized to the fullest extent. The establishment of an outpatient clinic as a part of the San Francisco Hospital, properly equipped and staffed, would involve great capital investment and high annual budget expenditure, much of which has been avoided by a fuller utilization of already existing facilities.

The Laguna Honda Home, formerly known as the Relief Home, provides institutional care for the chronic aged and infirm. The present plant, constructed during the past twelve years and one of the finest of its kind in existence (and to which will be added a new building), has a capacity of 2000 beds. From an institution giving custodial and ambulatory care primarily, with an infirmary providing hospital-type care for a small proportion of the Home's population group, there has developed the reverse condition during recent years. The institution is rapidly becoming one in which the hospital care for those affected by chronic diseases is of primary import

and the custodial type of care is less dominant. Recently, with the development of the pension program, many aged persons leave the Home to receive an old age pension and live outside the institution, with the result that frequently they require hospitalization on readmission to the Home. As in the case of the San Francisco Hospital, the visiting staff of the Home is made up of members of the faculties of the two medical schools, and the Home is one of the teaching institutions utilized in the curricula of the two schools. Admissions are arranged through the social service of the San Francisco Hospital.

The Hassler Health Home at present is a small (110 bed) institution, located in the hills of the peninsula about forty miles south of San Francisco, maintained for the care of the tuberculous of good prognosis. The persons cared for in the Home are of the younger age group and usually stay for periods of from six to 12 months. Selection is made in the wards of the tuberculosis division of the San Francisco Hospital, from which source all patients in the Home come.

The Emergency Hospital Service, in many cities more closely identified with the Police Department, is a unit within the Department of Public Health. Five units strategically placed operate on a full 24 hour basis and a sixth on week-end and holiday schedule, providing a radio-controlled ambulance service and first aid treatment by physicians assisted by nurses and stewards. No restrictions as to socio-economic status are applied to persons requiring emergency care, but the emergency hospitals are limited in scope of work to emergencies. If more than first aid is required, the patient's physician and the hospital of his choice are informed of the facts. If the patient has no physician or hospital choice, referral is made in rotation through lists of county medical society members and approved hospitals. Those who have no means of providing their own physician or hospital care are referred to the San Francisco Hospital and are admitted, except in emergencies, through the social service. The Emergency Hospital Service, medically staffed by young, well-trained physicians who have had good hospital background and rotate through the service on a two-year appointment usually, serves more than 65,000 persons annually.

Augmenting the San Francisco Hospital and the Emergency Hospital Service in providing a medical service in the home is the group of city physicians. These men, on part-time, long-term appointment, are available throughout the day and evening hours for any person who needs a physician in the home, but not necessarily hospital or even emergency hospital care. The city physician determines the need for hospital care or further home care, and no one is denied his request for one call, although repeat calls are not made if it is apparent that the person can afford his own medical attendant. Prescriptions written by the city physician are filled without cost in the pharmacy of the San Francisco Hospital.

So much for the Department of Public Health.

The Public Welfare Department

The Public Welfare Department was created by charter amendment in 1937, and, in its present set-up, combines the general relief program for the arbitrarily defined "unemployable unemployed" with the public assistance program for the needy aged, needy blind and dependent children. General relief to the unemployed, constituting the "employable" group, is administered in California as a state program, hence the breakdown into the artificial and arbitrary categories of "employable" and "unemployable" persons.

In the Public Assistance Division of the Public Welfare Department, more than 9,000 aged persons receive old age assistance, 450 blind receive blind aid, and 575 families including 1450 half-orphan children receive aid to dependent children, all outside institutions. The grants-in-aid for those under-privileged persons are made up of moneys from federal, state and local funds, under the federal social security act and the California welfare and institutions code. An additional group of dependent children receives aid from these same sources through the Juvenile Court, the division of administration of the program dating from 1913, 25 years ago.

In the Relief Division of the Department, approximately 3,400 cases representing about 5,700 persons, all found to be unable to carry employment, receive relief in the form of a check at semi-monthly intervals, and milk delivered daily to the home. A close working relation exists with the State Relief Administration in San Francisco, in that a common intake service obtains; each organization has its own district staff in the same district office; a common intercity service maintained by the Department serves both agencies in answering inquiries from other governmental units; and, of greater interest medically, the Central Medical Bureau serves recipients of relief from both agencies.

Central Medical Bureau

San Francisco, like other metropolitan areas throughout the nation, has in recent years been faced with the problem of providing medical care for the increasing number of persons receiving public assistance. This problem was recognized as far back as 1932. A committee was created to study the situation and to make recommendations to meet the need. This committee was composed of representative persons and included the deans of both local universities, the Director of Public Health, the president of the County Medical Society (who at that time was the Director of Public Health), other physicians who had served terms as presidents of state or local societies, a representative of labor, and one from the woman's clubs. The chairman was a layman who had had long experience as a member of the Board of Public Health. The recommendations of this committee resulted in the formation of the Central Medical Bureau.

The basic theory of operations for this bureau was to act as a central

medical intake for all cases receiving public assistance. It was to divide the medical case load into simple and complicated cases, treating the more simple at the bureau and referring the more complicated to existing clinic facilities throughout the city. In essence it was to be a " buffer " clinic and was intended to reduce the patient load in the already crowded outpatient system.

In addition the Bureau was to coördinate all existing public medical services in home, ambulatory and hospital care.

On this basis the Medical Bureau has been successfully operated for the past seven years. It has survived the changes of several administrations and has been financed at various times by the county, state and federal governments. In 1934 it received approval of the United States Public Health Service, which at that time was administering medical funds, to proceed as an experiment in medical relief. It was then taken over by the State Relief Administration.

The same medical director who developed the Bureau was kept in charge through these changes. He was originally selected upon the recommendation of the advisory committee. This committee has also been active throughout the existence of the Bureau, has acted in matters involving community policies, and has left the Bureau to do a medical job without evidence at any time of political interference. The quality of medical service produced has been excellent.

No attempt is made here to go into the details of operations of the clinic, as this is to be published in the near future in *Modern Hospital*. It would be well here to emphasize some of the outstanding facts about this Bureau which have made it unique in its field.

It offers a medical service to the entire case load with a minimum of delay. People receiving public assistance are eligible to receive care on the presentation of a card of identification, which is checked against a master file. This step requires only a few seconds.

From a professional point of view, all diagnostic work indicated can be performed; there is continuity of treatment from the home through the clinics to the hospital, and proper follow-up after discharge from the hospital.

There is a staff of 50 physicians who are paid salaries for part-time work. These are selected from the recent graduates of approved medical schools. They work an average of nine hours per week. This allows the younger physician to become established in the community and prevents clinic staleness. An important feature of the medical staff is the ability to expand and contract according to the case load. This feature prevents overloading with its possible consequences of reduced quality of medical care.

The Bureau has accumulated over 70,000 medical charts. They differ from the usual chart in that all home care, clinic and hospital information is included in the one chart. In addition, there may be social histories and a statement of medical-social problems. This is a necessity, for the social

treatment of an illness is often required to complete the physician's recommendations.

A close tie-in of the medical service has been effected by means of reports and conferences. In this way the one center is available for county, state and federal problems. The advantages of this can be readily seen as a saving to the taxpayer and a coördinated service when physical factors are concerned.

Because the Bureau serves an entire case load for all types of illnesses, the medical problems of the relief group are accurately exposed. Figures for several years reveal an incidence of illness approaching 20 per cent.

Costs are also accurately known. The complete service, which includes home and ambulatory medical care, dentistry, appliances, visiting nursing service, drugs, physicians' services, nurses, technicians, clerical help and overhead, costs in round figures about $18,000 per month. This amount is spent in the care of about 25,000 persons. The cost per person then for all services except hospitalization is approximately $9.00 per year. Hospital care is not included in this figure, being provided by the San Francisco Department of Public Health in the San Francisco Hospital.

While the Central Medical Bureau has received national recognition as an efficient system providing a good quality of medical care at a reasonable cost, there remain many possibilities for other developments. These would include expansion in the fields of rehabilitation by means of elective surgery, the development of a larger psychopathic unit to meet a special problem known to exist in the relief group, the consideration of providing intermediary type of hospitalization where indicated for subacute and chronic conditions, and home care for the aged.

There are also many opportunities for medical research with the group. The development of medical records which are cross-indexed with an available social history provides an abundance of material which may be used in various ways. It provides the opportunity not possible heretofore in metropolitan areas of following and studying a fixed and known section of the population.

Non-official services of considerable importance in the successful experience in San Francisco include the San Francisco County Medical Society, the Community Chest of San Francisco, the schools of medicine of the two universities, hospitals and outpatient clinics, and various voluntary hospitals and outpatient clinics.

The San Francisco County Medical Society has been alert to the community needs and problems to the extent of active interest and participation in community action to meet those needs. The society has been represented on the Health Council of the Community Chest, the Health Advisory Board of the Department of Public Health, and on the Central Medical Bureau Advisory Committee. The society's own committee on clinics and dispensaries has been of no little import to the Community Chest and the Department of Public Health in securing uniform practices and high stand-

ards in these institutions. The Director of Public Health, who served as the president of the society in the recent past and on the Medical Advisory Board of the Central Medical Bureau, Community Chest, etc., has given the Society many opportunities to participate in the planning of the department and members of the Society opportunities to serve on his consultant staff, paralleling the advisory committee on the Central Medical Bureau to the Public Welfare Commission and the State Relief Administration.

The Community Chest has had a rôle to play in the San Francisco experience in the relationship of its Health Council, made up of representatives of voluntary health agencies supported in part by the Chest, and its Hospital Council, made up of representatives of those hospitals receiving Chest support. The discussion of mutual problems with recognition of both community needs and limitations of official agencies, has fostered team work between official and non-official health and welfare agencies. Outpatient clinics of various hospitals have been able, through the councils, to arrive at interrelationships of importance in the whole plan, yet at the same time to preserve their own identity and autonomy in many respects.

As emphasized earlier, the members of the visiting staff of the San Francisco Hospital are members of the faculties of the University of California Medical School and the Stanford University School of Medicine. Over a period of many years, the working relations between the medical schools and the Department of Public Health have been close and of mutual value. During more recent years, there has developed a similar interrelation with the State Relief Administration and the Public Welfare Department. In any plan for a program of medical care at public expense, the teaching institutions must play important rôles. Large outpatient clinics maintained by the two universities as parts of their San Francisco plants are available and are being utilized by the community in the planned medical economy, with less expense to the local government and to the State Relief Administration than under another plan which would include setting up a new plant with overhead costs constituting a major item.

This same general statement of lowered costs to the relief agencies, due to already existing outpatient clinics maintained in the university hospitals, obviously holds true for the several other volunteer hospitals participating, on a contract basis, in the outpatient care of recipients of relief. The quality of their service, likewise, has been of high standard, and the service rendered has provided a real need in many instances because of religious and racial preferences. Here again the tolerant attitude has been manifest in the coördination of effort within the community so that the whole job might be done.

Discussion

As mentioned previously, San Francisco possesses many advantages since it is recognized as a medical center. The ratio of one physician to less than 500 people in the city, with two outstanding medical schools, to-

gether with several approved voluntary hospitals, all make for a high standard of medical practice. This is a highly important unit in the community's resources in the medical care program, and the solution of community problems. Add to these advantages the official health and welfare agencies of the local and state government, in which there has been relatively high stability and efficiency of administration and adequate financing, with a high degree of integration of planning and action. Under this system any person needing emergency or non-emergency medical care can secure that care through existing channels and facilities.

This does not mean that the existing facilities in San Francisco are entirely adequate to meet all medical needs as they arise without delays. There are several inadequacies which should be emphasized. Some of these have been pointed out and others are probably apparent to the student of these problems.

Perhaps the most outstanding gap involves the recipients of public assistance for the aged, the blind, the dependent children, and those on work relief (WPA, NYA, CCC). While medical-dental-nursing services are available, in a planned program, for recipients of general relief, there is no planned program available to the group receiving these allowances, recognized in some respects to be liberal, but recognized also to be insufficient to provide adequate medical care. The voluntary outpatient clinics, supported in part by the Chest, have been very much interested in meeting the need and have attempted to provide outpatient care as best they could at part-pay and free rates. In many instances, too, privately practicing physicians have contributed to these persons without regard to a fee. Hospital or custodial institutional care to these people is available, however, as it is to the recipients of relief and the medically indigent of the population as a whole.

It is worthy of note, however, that there is a definite difference between the various types of medicine. Even a short term experience in the private practice of medicine impresses the physician with the difference between "hospital" practice and "private" practice; not as many, perhaps, are familiar with the third type which might be termed "relief" medicine. In the person unemployed, and without financial resources, the interrelations of his physical status, the mental stress resulting from his present condition, looking to the unavoidable change in standard of living on relief at public expense, the outlook toward his fellowman, his family, and himself, all assume an importance that is not as significant, usually, in private practice. In "relief" medicine, however, the frequency of such reactions and their definite effects is more nearly the rule than the exception. In dealing with such problems, in the medical area, valuable assistance to the physician can be had from the social worker and from the psychiatrist. It is unfortunate that in many instances the physician is reluctant to recognize the social worker's capacities as a possible resource of value to him in his work. Many sociologic factors of moment unknown to the physician are available to him through the social worker, if only he would recognize her accessibility.

From the administrative point of view another inadequacy deserves mention: standards of need, residence, and other factors affecting eligibility to relief and medical care are not uniform, with the result that investigation and reinvestigation, to the confusion and dismay of the applicant, are unavoidable. Too many separate agencies, with individually different standards, are involved in the whole program. Legislative instruments may be changed and thereby permit some simplification, but these will have to be rather extensive to accomplish the objective.

A third important inadequacy in the San Francisco set-up is that of facilities for convalescent care. With excessive demands made on the San Francisco Hospital, long waiting lists for eligible applicants for admission are created and the patient's stay in the hospital is shortened, sometimes to the point where it is medically unsound to discharge the patient, with the result that he is sent to his home earlier than good medical practice would dictate. Not infrequently the convalescent patient's home is one presenting inadequate housing and other hazards, forcing incomplete or delayed recovery. The need for convalescent care is recognized as a pressing problem, and it is hoped that augmentation of existing physical plants, particularly in the recently planned revamping of the rôle of the Laguna Honda Home and the Hassler Health Home in the whole program, will permit the development of better facilities for convalescent care in the near future.

Summary

It must be apparent that certain desirable relationships between official and voluntary agencies exist in San Francisco. How have these relationships been developed? We believe that the answer to this question lies in three points which we have tried to bring out in this paper:

(1) The type of government in force in San Francisco with a relatively high stability of administration;

(2) The participation of the San Francisco County Medical Society in official and voluntary agencies' advisory boards and committees; and

(3) The general attitude of civic minded persons interested in the community and participating in the study and solution of health, welfare, and related problems, some of the most consistent attributes of which are tolerance, a desire to get at the facts, and true unity of effort to solve the problem.

Conclusion

Though limitations of budget, of planning, and of coördination are effective, San Francisco has made significant strides toward achieving the integrated medical program. The fact is emphasized that the medically indigent in San Francisco are given high standard medical care at public expense.

This article endeavors to demonstrate that hospitalization for the acute

and the chronic ill, home visits by physicians, certain outpatient facilities such as for maternity and the tuberculous, follow-up surgical services especially as to fractures, emergency and ambulance services, generalized nursing in certain districts, infant welfare service of varied character, dental care for special groups, and nutritional services for needy school children are all furnished for the indigent by the Department of Public Health. This program is further integrated by the supplying of food and other needs for the family by the Relief organization and outpatient clinic facilities by the State-supported Central Medical Bureau and by a number of hospitals supported by the Community Chest. Certain limitations and inadequacies are admitted. The moot question, however, still remains unanswered: Can other departments of health and communities assume similar responsibilities, and further, can a voluntary insurance plan be adopted for certain low income groups which would cover hospitalization, medical care to include the nurse, the druggist, and the dentist, and family security care for the period of illness? The Department of Public Health spends each year $4.228 per capita, the Community Chest $0.677, the Relief Agency $3.60, which includes the Central Medical Bureau, for this type of care for citizens of the City and County of San Francisco. This is a yearly per capita cost of $8.505, which does not truly represent medical costs since attending and consultant Stanford and California Universities' staffs serve without compensation in several city and county institutions, as do other physicians in several hospitals and clinics financially supported in part by the Community Chest.

CASE REPORTS

CONGENITAL HEMOLYTIC JAUNDICE; REPORT OF A CASE OF CONGENITAL HEMOLYTIC JAUNDICE; INITIAL HEMOLYTIC CRISIS OCCURRING AT THE AGE OF 75; SPLENECTOMY FOLLOWED BY RECOVERY *

By HARRY MANDELBAUM, M.D., *Brooklyn, New York*

CONGENITAL hemolytic jaundice presents several phases that deservedly attract wide interest. To the student of genetics there is offered a disease inherited as a true dominant character in accordance with the Mendelian principles of heredity (Naegli [21]). To the hematologist it affords the most classic example of true hemolytic anemia. To the internist the polymorphism of the presenting clinical picture, in many instances, differs so radically from the usual description of the disease as to tax his diagnostic acumen. However, the basic features are readily demonstrable and permit reasonable assurance in the diagnosis of congenital hemolytic jaundice. To the surgeon, splenectomy, the only remedial measure, offers a low operative hazard and is attended with exceedingly gratifying results.

Several names have been suggested to replace the usual one, "congenital hemolytic jaundice." Naegli [21] suggested "spherocytic anemia"; Krumbhaar,[13] "spherocytic icterus"; Whipple,[28] "typical hemolytic jaundice"; Fiessinger,[7] "familial hemolytic splenomegaly"; and others.

Congenital hemolytic jaundice was first described by Murchison [20] in 1885. Its familial character was reported in 1890 by Wilson [30] and again in 1900 by Minkowski.[17] Chauffard [1] in 1907 first directed attention to the microcytosis, increased fragility and reticulocytosis that characterize this disease and attributed the jaundice to active hemolysis. Naegli [21] became the vigorous exponent of the hereditary nature of the condition; he described the decreased diameter and increased thickness of the characteristic microcytes. Haden [9] measured this thickness and proved the close relationship between the point of initial hemolysis and the volume-thickness index.

Splenectomy offers the only cure for congenital hemolytic jaundice. It was first performed for this condition in 1907 by Vaquez and Giroux,[26] but the patient died. In 1911, Micheli [18] reported a remarkable cure following splenectomy in a patient with familial hemolytic icterus. Lord Dawson [4] credits Spencer Wales with having successfully performed splenectomy for hemolytic jaundice in 1887, without knowing the correct diagnosis at the time. At the Mayo Clinic, splenectomy has been done for this disease since 1911 (Pemberton [22]).

The criteria for establishing the diagnosis of congenital hemolytic jaundice

* Received for publication July 5, 1938.

applied to a patient, aged 75, presenting evidence of increased blood destruction, led to its recognition. Splenectomy resulted in an immediate arrest of the hemolytic crisis and a remarkable recovery.

Case Report

First Admission. Mrs. S. P., aged 75, was admitted to the Jewish Hospital of Brooklyn, January 13, 1937.

Past Personal History. Excepting childhood diseases, she had never been ill. She had never been jaundiced nor did she recall any history of jaundice affecting any of her relatives. She had always had a "sallow complexion."

Present Illness. Two weeks before admission she seemed to have lost her appetite completely. There was no nausea or vomiting, and no abdominal discomfort. Weakness and loss of weight necessitated her going to bed. After a week it was noted that she appeared more "sallow" than usual; there was no pruritus, the urine was not darker than usual and the stools were not clay-colored. A few days before admission headache appeared and increased in severity to such an extent that it dominated all other complaints when she entered the hospital.

Physical Examination. The patient appeared extremely weak. She was markedly anemic and obviously had lost considerable weight. The skin and sclera were slightly icteric; no scratch marks were seen. The heart by percussion measurements was slightly enlarged. The apical and radial pulse rate were 94. An extrasystole was noted every sixth or seventh beat. A rough systolic murmur was heard over the mitral area. The blood pressure was 132 systolic and 50 diastolic. The lungs showed nothing remarkable. The abdomen was soft. The liver was felt 3 cm. below the costal border; it was smooth and not tender. The spleen was felt 4 cm. below the costal border; it was firm and not tender. No masses or other organs were palpable. Neurologic examination was entirely negative.

Laboratory Summary. The urine concentrated well; no bile, albumin or sugar were reported. Urobilinogen was present in a concentration of 1:40 dilution units. The feces contained no ova or parasites; bile was present; in one specimen a trace of blood was detected. Roentgenologic survey of the gastrointestinal tract did not reveal any pathologic process. The gall bladder could not be visualized after double dye oral study. Gastric analysis (repeated twice) free HCl reached a concentration of 20; combined acidity, 36; blood was found in traces. Blood chemistry: sugar, 119 mg. per cent; urea nitrogen, 20 mg. per cent. Icteric index, 20. Van den Bergh, direct, biphasic; indirect, 4.1 units per 100 c.c. of serum. Blood count: red cells, 1,920,000; hemoglobin, 38 per cent; color index almost one; white cells, 3,700; platelets appeared to be present in less concentration than normally. Morphologic blood study: neutrophiles, 51 per cent; eosinophiles, 1 per cent; lymphocytes, 45 per cent; monocytes, 3 per cent; reticulocytes, 1.8 per cent; marked anisocytosis and poikilocytosis, positive hyperchromia, moderate number of macrocytes and microcytes; no punctate basophilia, no nucleated reds. Bleeding time, two minutes; tourniquet test, positive; coagulation time, 3 minutes. Fragility test: normal (see table 4).

Course. Repeated blood studies suggested pernicious anemia, but the presence of free HCl in the gastric juice definitely ruled this out. No evidence of malignancy was obtained. The occasional microcyte, while suggestive, was not conclusive in the presence of normal fragility. Liver extract was given parenterally, daily. Five days after admission, the reticulocyte count * increased to 12 per cent, the hemoglobin increased to 42 per cent; the red blood cells totaled 2,200,000; color index, 0.95. Patient was discharged January 27, 1937.

Second Admission. Mrs. P. was readmitted to the Jewish Hospital July 19, 1937.

* The reticulocyte increase occurred 48 hrs. after the first injection of liver extract.

After her discharge from the hospital she had been given (by her son, a physician) injections of liver extract once a week for two months. She gradually regained her weight and strength. A month before readmission her son observed that she had again lost her appetite; she became weak, lost weight, and complained of headache. She appeared anemic and slightly jaundiced. Liver extract was injected daily, but the anemia progressively increased, headache became unbearable and general weakness marked. There was no abdominal pain, nausea or vomiting. Dyspnea and palpitation followed slight effort, and ankle edema appeared upon dependency.

Physical examination. Mrs. P. appeared extremely weak and emaciated. Anemia was marked. The skin and sclera were icteric ++; no scratch marks were visible. Moderate orthopnea was present; the percussion outline of the heart was enlarged; the sounds were of poor muscular tone; a soft mitral systolic murmur was heard; many extrasystoles were noted. The apical rate was 100; the blood pressure was 118 systolic and 74 diastolic. Coarse râles were evident over both bases. Ankle and sacral edema were present. The abdomen was soft. The liver was felt 7 cm. below the costal arch and was tender. The spleen was felt 6 cm. below the costal edge, was firm and not tender.

Laboratory Summary. The urine showed no bile, albumin or sugar; urobilinogen was reported in a concentration of 1:40 dilution units. The feces showed bile, and traces of blood were occasionally found. Blood chemistry: sugar, 108 mg. per cent; urea nitrogen, 10.5 mg. per cent; cholesterol, 376 mg. per cent. Icteric index, 25. Van den Bergh, direct, biphasic; indirect, 10 units per 100 c.c. of serum (for further studies see table 3). Roentgen study of the long bones failed to reveal findings suggestive of metastatic malignancy. Blood count on admission: red cells, 1,320,000; hemoglobin, 30 per cent; color index, 1.1; white cells, 5,400. Morphologic blood study: neutrophiles, 80 per cent; lymphocytes, 20 per cent; moderate anisocytosis, poikilocytosis and polychromatophilia; macrocytes ++; microcytes, ++; no nucleated red cells; reticulocytes 28.6 per cent; fragility increased (table 4).

Course. Five hundred cubic centimeters of whole blood were transfused on July 21, and again on July 26. As shown in table 1, the hemolysis continued so actively

TABLE I

During an Acute Hemolytic Crisis, Transfusion Effects But a Brief Check to the Advancement of the Anemia.

Date 1937	Hemoglobin Sahli	Erythrocyte count	Color index	Leukocyte count
July 19	30%	1,320,000	1.1%	5,400
July 21		Transfusion 500 c.c. citrated blood		
July 23	37%	1,680,000	1.1%	9,400
July 26		Transfusion 500 c.c. citrated blood		
July 27	35%	1,430,000	1.2%	9,500
July 28	34%	1,340,000	1.3%	5,200

that each transfusion effected but a temporary respite from the increasing anemia. The presence of acute hemolytic anemia, acholuric jaundice without pruritus, bilirubinemia, increased urobilinogen in the urine and characteristic Van den Bergh reactions; a microcytosis in the presence of marked anemia, with attendant increased fragility to hypotonic salt solutions; reticulocytosis; and splenomegaly, were dependable criteria for establishing the diagnosis of congenital hemolytic jaundice in the stage of acute hemolytic crisis. Splenectomy was suggested as the only measure available. Daily transfusions of 300 c.c. of citrated blood were given, and when the hemoglobin was brought up to 56 per cent and the red blood cells to 2,700,000, she was considered a safe surgical risk (table 2).

TABLE II

Preoperative and postoperative blood studies. Note difficulty in raising the hemoglobin and red blood cell values before splenectomy. Within three days after operation, the concentration of red blood cells was increased by over a million. The effect of a number of complications accompanied by pyrexia was a gradual lowering of the hemoglobin and erythrocyte concentration. Compare the immediate response following transfusion October 1 with that shown in table 1.

Date 1937	Hemoglobin Sahli	Erythrocyte count	Leukocyte count	Poly. neut.	Eosin.	Lymph.	Mono.	Addenda
Aug. 4	23%	900,000	4,700	55%	2%	47%	1%	Retic. 39.3%
Aug. 4	Transfusion 300 c.c. citrated blood.							
Aug. 5	Transfusion 300 c.c. citrated blood.							
Aug. 6	Transfusion 300 c.c. citrated blood.							
Aug. 7	40%	1,780,000						
Aug. 7	Transfusion 300 c.c. citrated blood.							
Aug. 8	Transfusion 300 c.c. citrated blood.							
Aug. 9	Transfusion 300 c.c. citrated blood.							
Aug. 9	53%	2,470,000						Coag. time 2 min.
Aug. 10	Transfusion 300 c.c. citrated blood.							
Aug. 10	53%	2,230,000						
Aug. 11	Transfusion 300 c.c. citrated blood.							
Aug. 11	56%	2,700,000						
Aug. 12	Preoperative transfusion 300 c.c. citrated blood.							
Aug. 13	67%	2,640,000	6,100	85%		15%		Retic. 20%
Aug. 14	70%	2,960,000	9,850	92%	2%	6%		Platelets 145,000
Aug. 16	70%	2,850,000	8,800	93%		7%		Retic. 2.3%
Aug. 17	70%	3,180,000	7,800					
Aug. 19	67%	3,450,000	7,600	82%		16%	2%	Microcytes++
Aug. 20	70%	3,850,000	9,450	72%	2%	20%	6%	Retic. 1.8%
Aug. 21	67%	3,850,000						
Aug. 24	70%	3,450,000	8,100					
Aug. 25	59%	3,090,000	8,850					Acute cholecystitis.
Aug. 28	60%	2,780,000						
Aug. 29	59%	2,900,000						
Aug. 30	53%	2,330,000						
Aug. 31	50%	2,690,000	7,800	58%	8%	26%	8%	Microcytes++
Sep. 1	56%	3,550,000						
Sep. 2	50%	2,240,000						Onset of phlebitis.
Sep. 3	56%	2,280,000	9,800	70%	4%	21%	4%	1% myelocytes
Sep. 5	54%	2,300,000						
Sep. 8	51%	2,550,000	9,100	54%		38%	8%	
Sep. 14	62%	2,310,000	7,500	78%	2%	18%	2%	
Sep. 20	54%	2,750,000	17,400	78%	1%	19%	2%	Acute cystitis.
Sep. 22	50%	2,660,000	13,100	76%	3%	16%	5%	Microcytes++
Sep. 27	46%	2,690,000	10,200	48%	5%	32%	10%	
Sep. 30	53%	2,570,000	14,700					
Oct. 1	Transfusion 300 c.c. citrated blood.							
Oct. 2	70%	3,670,000						
Oct. 6	65%	3,330,000	12,500	59%	8%	27%	1%	5% basophiles
Oct. 12	56%	2,960,000	6,500	40%	5%	51%	3%	1% basophiles
Nov. 3	65%	3,400,000	11,300	33%	8%	48%	9%	2% basophiles
Mch. 28, 1938	60%	2,900,000	9,400	38%	5%	55%	2%	Retic. 2%
May 17, 1938	68%	3,300,000	16,400	45%	5%	36%	11%	3% basophiles Retic. 1%

Operation. Dr. B. Kogut, August 12, 1937. Avertin and ether anesthesia. On opening the peritoneum there was an escape of some thin serous fluid. The uterus was small. The stomach appeared normal and careful palpation failed to reveal any lesion. The gall bladder was enlarged and tense; no stones were palpable. The pancreas was essentially normal. The liver was somewhat enlarged; many fibrous streaks were present, giving the liver a gray color. The spleen was considerably enlarged, about three times its normal size; many fibrous strands were evident. A small accessory spleen was found just posterior to the hilus of the spleen proper. The spleen and accessory spleen were removed.

Pathological report. Dr. Max Lederer. The specimen consists of a spleen 18 by 13 by 6 cm., weighing 650 gm. The external surface is purple and roughened by delicate pink tags. There is a raised yellow area, 1.5 by 1 cm. The cut surfaces are brown-red; the Malpighian corpuscles and fibrous markings are prominent. The pulp does not scrape easily. The raised yellow area, above described, extends 1.2 cm. below the external surface. The accessory spleen measures 2 cm. in diameter and has the general characteristics of the spleen proper. Microscopic study: The trabeculae of the spleen appear thickened. The Malpighian bodies are fairly large and well spaced; some have active germinal centers. There is an increase in the reticuloendothelial elements. The sinusoids are distended and their lining cells prominent; some are empty, others contain a large number of red blood cells, large mononuclear cells, eosinophiles and a few polymorphonuclear leukocytes. Occasional megakaryocytes are seen. Scattered throughout the preparation is a great deal of golden brown pigment; this is both extracellular and intracellular (contained within large mononuclear cells). With the Perl stain, this pigment is seen to contain iron. Sections through the raised yellow area described above show zones in which only a faint outline of the former cytoarchitecture is seen. In and about these zones there is round cell infiltration. Diagnosis: The histologic picture is compatible with the diagnosis of congenital hemolytic jaundice; a small infarct is present.

Postoperative course. The patient reacted well for the first 24 hours; then auricular fibrillation was noted, with an apical rate of 120 and a radial pulse of 110. The blood pressure remained about 120 systolic and 80 diastolic during this period and continued so throughout her hospital stay. The heart responded well to digitalis. The temperature rose to 102° F. postoperatively and continued at about this level for 36 hours; then it ranged between 100° F. and 101° F. for the succeeding 12 days. On August 20 (eight days postoperatively), examination of the lungs showed dullness, diminished breathing, and fine crepitant râles over the left base. Two days later physical signs of a left pleural effusion, reaching to the inferior angle of the scapula, were obtained; the heart was displaced slightly to the right. The heart rate was maintained at 78; auricular fibrillation was still present; there was no pulse deficit; the cardiac sounds were of good quality; sacral edema was slight. Resorption of the effusion was complete by August 25, at which time the jaundice had appreciably decreased; the heart was no longer fibrillating; an occasional extrasystole was present; there was no sacral edema; the liver edge was palpated at the costal border. That evening (August 25), the patient complained of abdominal pain and vomited. The temperature rose to 102.4° F. The following day the gall bladder could be felt, distended and tender; the jaundice again deepened; the icteric index increased from 13.3 to 31.5 (see table 3) and bile appeared in the urine for the first and only time. The temperature continued intermitting up to 102° F. until August 28, then ranged between 99° F. and 100° F. for the next three days; epigastric pain continued and repeated vomiting necessitated parenteral saline injections to maintain water and electrolyte balance. By September 3 abdominal pain and vomiting had ceased, the gall bladder was no longer palpable, and the jaundice was receding.

During the next three weeks (September 1 to September 21), the temperature

ranged between 99° F. and 102° F. daily. Phlebitis of the left internal saphenous vein had developed; the vein was exquisitely tender in the middle third of the thigh, with edema extending from the middle of the thigh to the base of the toes. Blood cultures taken during this period were subsequently reported negative. Ice bags were applied to the vein and the leg was elevated; edema and tenderness gradually abated.

From September 21 to October 1 the temperature did not rise above 101° F. An acute cystitis developed; dysuria and frequency disturbed the patient considerably. Mandelic acid therapy effected a cure.

The succession of complications had rendered the patient weak and exhausted. A transfusion of 300 c.c. of blood was given October 1, the first since her operation. She improved rapidly. The temperature remained normal after October 4; she was permitted out of bed after another week and discharged from the hospital October 13, 1937.

TABLE III

Icteric index and Van den Bergh studies. Sharp rise on August 27 was associated with symptoms and physical signs of gall bladder affection.

	Date 1937	Icteric Index	Van den Bergh	
			Direct	Indirect
Pre-operative	July 21	24.2		
	July 26	25	Biphasic	10 units
Postoperative	Aug. 16	14.3		
	Aug. 20	13.3		
	Aug. 23	13.3	Biphasic	4.1 units
	Aug. 27	31.5	Biphasic	5.1 units
	Aug. 30	23	Biphasic	4.4 units
	Sep. 2	22.2	Biphasic	4.8 units
	Sep. 9	14.2	Biphasic	4.8 units
	Sep. 13	16.4		
	Sep. 17	14	Biphasic	4 units
	Oct. 6	13.8		
	Oct. 12	14		

Subsequent course. Following her discharge from the hospital she continued to improve, gradually regaining her weight and strength. She resumed her customary activity. There has been no recurrence of the biliary dyspepsia. She has maintained (without hematinics) a hemoglobin above 65 per cent and a red blood cell count above 3,000,000. Blood count and morphologic studies done May 17, 1938 (nine months postoperative) showed the following: red cells, 3,300,000; hemoglobin, 68 per cent; white cells, 16,400; neutrophiles, 45 per cent; eosinophiles, 5 per cent; lymphocytes, 36 per cent; monocytes, 11 per cent; basophiles, 3 per cent; moderate chromatophilia, slight anisocytosis, few macrocytes, moderate number of microspherocytes and one nucleated red cell; reticulocytes, 1 per cent. Increased fragility of the red cells was still present (see table 4). Icteric index, 7 (May 18, 1938).

DISCUSSION

Congenital hemolytic jaundice is an inherited familial disease. It can occur in either sex of any race at any age. While most cases give rise to symptoms leading to their recognition in early adult life (Kracke and Garver [12]), cases

TABLE IV

Fragility tests done on patient and control. Creed [2] has shown that anemia of itself increases the resistance to hypotonic salt solutions and must be taken into account in interpreting the fragility curves.

Date	Unwashed Cells				Washed Cells			
	Patient Hemolysis		Control Hemolysis		Patient Hemolysis		Control Hemolysis	
	begins	complete	begins	complete	begins	complete	begins	complete
1-14-37	0.46	0.36	0.46	0.34	0.46	0.32	0.46	0.34
8-9-37	0.60	0.38	0.46	0.32	0.56	0.44	0.46	0.34
8-25-37	0.52	0.38	0.46	0.34	0.52	0.38	0.46	0.32
10-14-37	0.52	0.32	0.44	0.34	0.52	0.32	0.44	0.32
5-18-38	0.50	0.34	0.44	0.32	0.50	0.34	0.44	0.32

have been recognized at birth (Gänsslen [8]); in Thompson's series,[25] the youngest was six weeks and the oldest, 58 years.

Clinical features. The outstanding characteristics of congenital hemolytic jaundice are the chronic acholuric (dissociated) jaundice without pruritus, persistent enlargement of the spleen and hemolytic anemia. In many cases there is an overemphasis of one or the other of the cardinal features: the splenomegaly may be out of proportion to the degree of anemia and jaundice; the spleen may occupy the greater part of the abdomen and extend to the pelvic brim. Pigment stones, which are frequently present in this disease (68.6 per cent of the cases reported by Pemberton [22]), may lead to gall stone colic and obstructive jaundice. The anemia is usually of the hyperchromic type and may be mistaken for pernicious anemia, especially when the color index is above one and an abundance of red blood cells, larger than normal erythrocytes, are seen; most of these large cells may be identified as reticulocytes when brilliant cresyl blue is used as a vital dye (Thompson [25]).

The pathognomonic findings in congenital hemolytic jaundice. (*a*) The microspherocyte: The basic cellular change in this disease is the presence of specific red blood cells which are characteristically more spheroid in shape, their diameter smaller than normal, and their thickness greater than normal. The volume-thickness index of Haden is increased. They vary in number and it is thought that their sudden increase in the blood stream may lead to increased activity of the spleen and result in an acute hemolytic crisis. Haden,[9] Thompson,[25] Krumbhaar [13] and others have stated their conviction that the microspherocyte is an inherited variant from normal. It is frequently associated with other anomalies, such as the "tower skull" described by Gänsslen.[8] (*b*) The increased fragility of the red blood cells: Haden [9] has conclusively proved the relationship between the size and shape of the red cells (the volume-thickness index) and their hemolytic reaction to hypotonic saline solutions. His work leaves no doubt that the spherical microcytes alone are responsible for the increased fragility that characterizes congenital hemolytic icterus.

The rôle of the spleen. The spleen is an area of concentration along the line of the reticulo-endothelial system. Under physiologic conditions there is main-

tained in health a balance between bone marrow hematopoiesis and the splenic function of cell storage and cell destruction; the term hemolytopoietic balance was suggested by Krumbhaar.[14] It is believed that the presence of microspherocytes in the circulating blood stimulates the spleen to increased activity. Klemperer [11] believes this to be due to a reflex mechanism resulting in an active hyperemia of the spleen that leads to hyperplasia. The spleen becomes enlarged and markedly hyperemic; there is striking engorgement of the reticular meshes of the red pulp. This engorgement provides the opportunity for increased blood destruction by the macrophages of the splenic pulp. To maintain a hemolytopoietic balance, the bone marrow increases its erythrogenic activity; this is evidenced in the peripheral blood by reticulocytosis, leukocytosis, anisocytosis, polychromasia and the presence of nucleated red blood cells. In the presence of a severe hemolytic crisis, the bone marrow is stimulated to even greater activity; this is reflected in the myelogram (table 5), which shows a marked increase in

TABLE V

Myelogram and concomitant blood smear studies by Dr. M. Morrison. Note marked hyperactivity in erythrogenesis as revealed by the bone marrow smear preoperatively.

			Normal values	Preoperative Aug. 6, 1937	Postoperative Sep. 10, 1937
Bone Marrow Smears	Granulocytes	Myeloblasts	0–5%	11%	1%
		Myelocytes	25–36%	22%	42%
		Metamyelocytes	5–10%	6%	4%
		Eosinophilic myelocytes	0–1%	2%	4%
		Staff cells	0–5%	26%	10%
	Lobocytes	Polymorphonuclear neutrophiles	45–50%	26%	35%
		Eosinophiles	0–1%	7%	3%
		Lymphocytes	5–10%	0%	1%
		Monocytes	1–2%	0%	0%
		Granulocyte : lobocyte ratio	55 : 45	67 : 33	61 : 39
		Granulocyte : erythroid ratio	90 : 10	15 : 85	68 : 32
		Early : late cell ratio	10 : 90	60 : 40	50 : 50
Concomitant Blood Smears		Polymorphonuclear neutrophiles		70%	72%
		Eosinophiles		2%	0%
		Staff cells		0%	6%
		Lymphocytes		22%	18%
		Monocytes		6%	4%
		Anisocytosis		++++	++
		Poikilocytosis		++++	++
		Polychromasia		+++	++
		Macrocytes		+	+
		Microcytes (spherical)		++	++

the erythrogenic function of the bone marrow, and in the hemogram, where young red cells are in abundance; a reticulocytosis (up to 50 per cent) and a marked leukocytosis (as high as 50,000) have been reported.

Clinical course. In some, symptoms are manifest at birth: in others, the disease may not appear until early childhood or adult life; in still others, it may never appear in such outspoken form as to be recognized (Gänsslen [8]). Such latent cases may never show clinical symptoms of the disease and may live active lives; many show a peculiar pallor which is usually considered to be their natural

color. The blood of these patients shows the characteristic microspherocytes and exhibits the increased fragility reactions. Little is known about those factors which initiate the excessive hemolysis that signals the onset of the active disease. The latent cases may become active at any time during their life; in Thompson's cases,[25] the age at which activity began varied from six months to 59 years. Once the disease becomes active, spontaneous remissions and recurrences alternate and chronic anemia and jaundice persist until splenectomy. These recurrences (acute hemolytic crises) interrupt the otherwise placid course of the disease and are characterized by an acute onset with rapidly increasing anemia and jaundice; the degree of anemia and bilirubinemia are proportionate to the extent of red blood cell destruction; the spleen increases in size, indicative of its increased activity; the urine and feces show an increased excretion of urobilinogen.

Treatment. Splenectomy is generally accepted as the only remedial measure applicable to cases of congenital hemolytic jaundice. It is indicated when the diagnosis is established. It has proved most valuable as an emergency measure in critical severe hemolytic anemias (Doan and his associates [5]). It removes a large part of the erythro-phagocytic mechanism and permits the maldeveloped erythrocyte to remain and function longer in the circulating blood; the bone marrow is thus better able to contribute its physiologic rôle to the hemolytopoietic balance. Splenectomy effects immediate relief; the already overactive bone marrow rapidly raises the concentration of the circulating red blood cells. Moore and Doan [19] observed an immediate postsplenectomy rise of a million erythrocytes; they attributed this to contraction of the spleen. The hemogram, after splenectomy, continues to show microspherocytes and young red blood cells, but in less concentration; the increased fragility, while not as marked as previously, never completely disappears. Lord Dawson,[3] in referring to the case operated upon by Spencer Wales in 1887, stated that he had been able to demonstrate increased fragility in this patient 27 years later. Splenectomy does not remove the inherited abnormality, the faulty red blood cell. Lord Dawson [4] reported that he had observed cases where removal of the spleen was ineffective and increased blood destruction continued. It is advisable, at operation, to search for accessory spleens, and to remove them, if found. This is as applicable in congenital hemolytic jaundice as it has been proved to be in essential thrombocytopenic purpura (Morrison and associates [18]).

Acquired hemolytic jaundice. The so-called acquired form of hemolytic jaundice was first described by Widal [29] in 1907. It covers a number of hemolytic conditions of varied nature. Most competent authorities doubt the existence of an acquired type. Whipple and his associates [28] classify their cases of hemolytic jaundice as typical and atypical. The typical group conformed to the criteria pathognomonic of congenital hemolytic jaundice. In the atypical group reported by Thompson,[25] there were 15 cases. Four, all elderly, were proved to have reticulum cell sarcoma of the spleen. Two patients presented the syndrome in association with positive blood Wassermanns; antiluetic treatment cured them. One case at autopsy showed extensive tuberculosis with active involvement of the spleen. Four other cases had submitted to splenectomy, without improvement. Kracke and Garver [12] consider the so-called acquired cases of hemolytic jaundice as true latent cases which have become activated by intercurrent infection, trauma, tuberculosis, syphilis, malaria, etc. Meulengracht,[15] however, be-

lieves that acquired hemolytic jaundice is an entity. He reported three cases in patients past 40 who presented all the clinical features of the disease. In none of these patients were any spherical microcytes present, although the red blood cells showed increased fragility to hypotonic salt solutions. He attributed the pathologenesis in these cases to the spleen and reported recovery following splenectomy.

Case discussion. The problem presented for diagnosis was one of hemolytic anemia with jaundice and splenomegaly. The degree of anemia, the leukopenia, the slight icterus, the color index of 1.0, a palpable spleen and the abundance of macrocytes were suggestive of pernicious anemia; the presence of free HCl removed this possibility from further consideration.

The general appearance suggested malignancy. It is well recognized that profound changes often take place in the blood of patients suffering from malignant tumors with extensive metastasis to the bone marrow. Waugh [27] reported cases where severe hemolytic anemia was present. Kiser and Rosenak [10] reported a similar case. Roentgenologic investigation of the gastrointestinal tract and long bones in the present case failed to reveal any suspicion of malignancy.

The morphologic blood studies done on the first admission were not conclusive; microcytes were not prevalent, the percentage of reticulocytes was slightly increased, and the fragility test was normal. Scott [23] has observed that during an acute hemolytic crisis the reticulocyte count may be low, rising sharply after the crisis had passed. Thompson [24] noted that while the fragility was increased in most cases of congenital hemolytic jaundice it varied in degree in different persons and in the same person at different times. He reported a case where the fragility was normal before splenectomy and only after operation was the characteristic increased fragility obtained. Doan, Curtis and Wiseman [5] also state that microcytosis, reticulocytosis and increased fragility changes may not be present during the acute crisis.

Krumbhaar,[13] Kracke and Garver [12] and Thompson [25] concur in the observation that while the hemolytic tendency in patients with congenital hemolytic jaundice may remain latent for years, once activity has become manifest, spontaneous remissions are common. Thus a remission occurring spontaneously five months after hemolytic anemia had first appeared suggested a diagnosis of typical rather than atypical hemolytic jaundice. Many microcytes were noted in the morphologic blood study and their spherical shape recognized in wet preparations. The increased fragility of the red blood cells to hypotonic salt solutions added security and confidence to the diagnosis of congenital hemolytic jaundice. The severity of the hemolytic crisis made it imperative to remove the offending spleen, despite the age of the patient. The remarkable success that splenectomy achieved was most gratifying. Subsequent blood studies (the last was taken eight months postoperatively) showed microspherocytes still to be present, but in less concentration, and the attendant increased fragility likewise present.

Summary

A case of congenital hemolytic jaundice has been presented. The disease remained latent until the patient had passed the seventy-fifth year; then activity was first manifested in an attack of acute hemolytic anemia. A recurrence occurred five months later, with alarmingly increasing anemia.

In the presence of a true hemolytic anemia, the identification of spherical microcytes and the demonstration of their increased fragility to hypotonic saline solutions may be considered pathognomonic of congenital hemolytic jaundice. These findings formed the basis for establishing the diagnosis in this case.

In the presence of a severe hemolytic crisis, splenectomy offers the only measure that can promptly terminate the excessive red blood destruction. The remission that splenectomy effected in this case was truly remarkable.

The demonstration of characteristic spherical microcytes, and their attendant increased fragility to hypotonic salt solutions, eight months after splenectomy, serves again to emphasize the true constitutional nature of the defect in the red blood cells that characterizes congenital hemolytic jaundice.

Note. Patient died 18 months after operation, from cerebral apoplexy.

BIBLIOGRAPHY

1. Chauffard, M. A.: Pathogénie de l'ictère congénital de l'adulte, Semaine médicale, 1907, xxvii, 25.
2. Creed, C. F.: Estimation of fragility of red blood corpuscles, Jr. Path. and Bact., Edinburgh, 1938, xlvi, 331.
3. Dawson, Lord: Hemolytic jaundice, Proc. Roy. Soc. Med., Clinical Section, 1913–1914, vii, 101.
4. Dawson, Lord: Indications for and results of removal of spleen, Brit. Med. Jr., 1932, ii, 699.
5. Doan, C. A., Curtis, G. M., and Wiseman, B. K.: The hemolytic equilibrium and emergency splenectomy, Jr. Am. Med. Assoc., 1935, cv, 1567.
6. Eppinger, H.: Die hepato-lienalen Erkrankungen, 1926, Julius Springer, Berlin.
7. Fiessinger, N.: Société médicale des hôpitaux de Paris. Report of May 15, 1936 meeting, Jr. Am. Med. Assoc., 1936, cvii, 513.
8. Gänsslen, M.: Hemolytic jaundice, Deutsch. Arch. f. klin. Med., 1922, cxl, 210.
9. Haden, R. L.: The mechanism of increased fragility of the erythrocyte in congenital hemolytic jaundice, Am. Jr. Med. Sci., 1934, clxxxviii, 441.
10. Kiser, E. F., and Rosenak, B. D.: Myelophthisic anemia in a case of carcinoma of the stomach, Jr. Am. Med. Assoc., 1936, cvii, 963.
11. Klemperer, P.: The pathologic anatomy of splenomegaly, Am. Jr. Clin. Path., 1936, vi, 99.
12. Kracke, R. R., and Garver, H. E.: Diseases of the blood and atlas of hematology, 1937, J. B. Lippincott Company, Philadelphia.
13. Krumbhaar, E. B.: Hemolytic jaundice. Spherocytic icterus, Jr. Am. Med. Assoc., 1936, cvii, 1739.
14. Krumbhaar, E. B.: The hemolytopoietic system in the primary anemias with a further note on the value of splenectomy, Am. Jr. Med. Sci., 1923, clxvi, 329.
15. Meulengracht, E.: Handbook of hematology. Edited by Hal Downey, 1938, Paul B. Hoeber, New York, p. 2283.
16. Micheli, F.: Unmittelbare Effekte der Splenektomie bei einem Fall von erworbenem Ikterus. Typus Hayem-Widal, Wien. klin. Wchnschr., 1911, xxiv, 1269.
17. Minkowski, O.: Über eine hereditäre unter dem Bilde eines chronischen Ikterus mit Urobilinurie, Splenomegalie und Nierensiderosis verlaufende Affection, Verhandl. d. Kong. f. inn. Med., Wiesbaden, 1900, xviii, 316.
18. Morrison, M., Lederer, M., and Fradkin, W. Z.: Accessory spleens. Their significance in essential thrombocytopenic purpura hemorrhagica, Am. Jr. Med. Sci., 1928, clxxvi, 672.
19. Moore, C. V., and Doan, C. A.: Mechanism of post-splenectomy erythroid reequilibration, Jr. Am. Med. Assoc., 1936, cvi, 325.

20. MURCHISON, C.: Clinical lectures on diseases of the liver and jaundice. Edited by L. Brunton, London, 3rd Edition, 1885.
21. NAEGLI, O.: Blutkrankheiten und Blutdiagnostik, 1931, Julius Springer, Berlin.
22. PEMBERTON, J. J.: Results of splenectomy in splenic anemia, hemolytic jaundice and hemorrhagic purpura, Ann. Surg., 1931, xciv, 755.
23. SCOTT, A. M.: Acholuric jaundice, Lancet, 1935, ii, 872.
24. THOMPSON, A. P.: Acholuric jaundice and increased fragility of the red blood corpuscles appearing after splenectomy, Lancet, 1933, ii, 1139.
25. THOMPSON, W. P.: Hemolytic jaundice, Jr. Am. Med. Assoc., 1936, cvii, 1776.
26. VAQUEZ, H., and GIROUX, R.: Ictere chronique acholurique avec splenomegalie; ses relations avec l'anémie hemolytique, Bull. et mém. Soc. méd. d. hôp. de Paris, 1907, xxiv, 1184–1192.
27. WAUGH, T. R.: Hemolytic anemia in carcinomatosis of the bone marrow, Am. Jr. Med. Sci., 1936, cxci, 160.
28. WHIPPLE, A. O.: Studies in splenopathy, Jr. Am. Med. Assoc., 1936, cvii, 1775.
29. WIDAL, F., ABRAMI, P., and BRULE, M.: Pluralité d'origine des icteres hemolytiques recherches cliniques et expérimentelles, Bull. et mém. Soc. méd. d. hôp. d. Paris, 1907, xxvii, 1354–1367.
30. WILSON, C.: Hereditary enlargement of the spleen, Brit. Med. Jr., 1890, i, 782. Lancet, 1890, i, 751.

HISTOLOGICALLY NON-MALIGNANT METASTASIZING HEMANGIOMA, WITH REPORT OF A CASE*

By MAURICE JAMES ABRAMS, M.D., *Brewton, Alabama*

THE rarity of this condition might not alone be sufficient reason for reporting a case, were its interest not heightened by the unusual and misleading diagnostic problem presented.

CASE REPORT

The patient was a white man, 35 years old, who was admitted to the Medical Service of the University Hospital on January 19, 1932. The circumstances prompting his admission will be described later.

His father died of tabes at 49 years; his mother was living and outwardly well at 60 years of age, though her Wassermann reaction was four plus. Her first two children were stillborn and the patient was her third child. During his infancy he apparently had congenital syphilis which was manifested by desquamation, bullae and loss of nails. Though untreated, he survived, and with the exception of a swelling of the right testicle at 10 years, his childhood and adolescence were not remarkable.

He was married at 21 years of age, and an only child was born one year later. The Wassermann reaction of this child at the present time is negative.

A review of his past history reveals positive findings only in the respiratory and gastrointestinal systems. In 1918, at 21 years of age, he developed a slight hacking cough which was unproductive and not associated with loss of weight, fever, night sweats, or chest pains. This cough persisted unchanged until 1923 when hemoptysis and productivity appeared. The hemoptyses were consistent but very slight, being described by the patient as "only a drop or two with each expectoration." The amount of blood, however, gradually increased, so that every productive cough brought

* Received for publication April 11, 1938.
From the Medical Service of the University Hospital, University of Maryland Medical School.

up sufficient blood to distinctly color the sputum. There were occasional remissions never exceeding three days, during which his cough became minimal and the sputum almost blood free.

In 1927, nine years after the onset of the cough, and four years after the beginning of his hemoptyses he first experienced pain in his chest. The pain was bilateral,

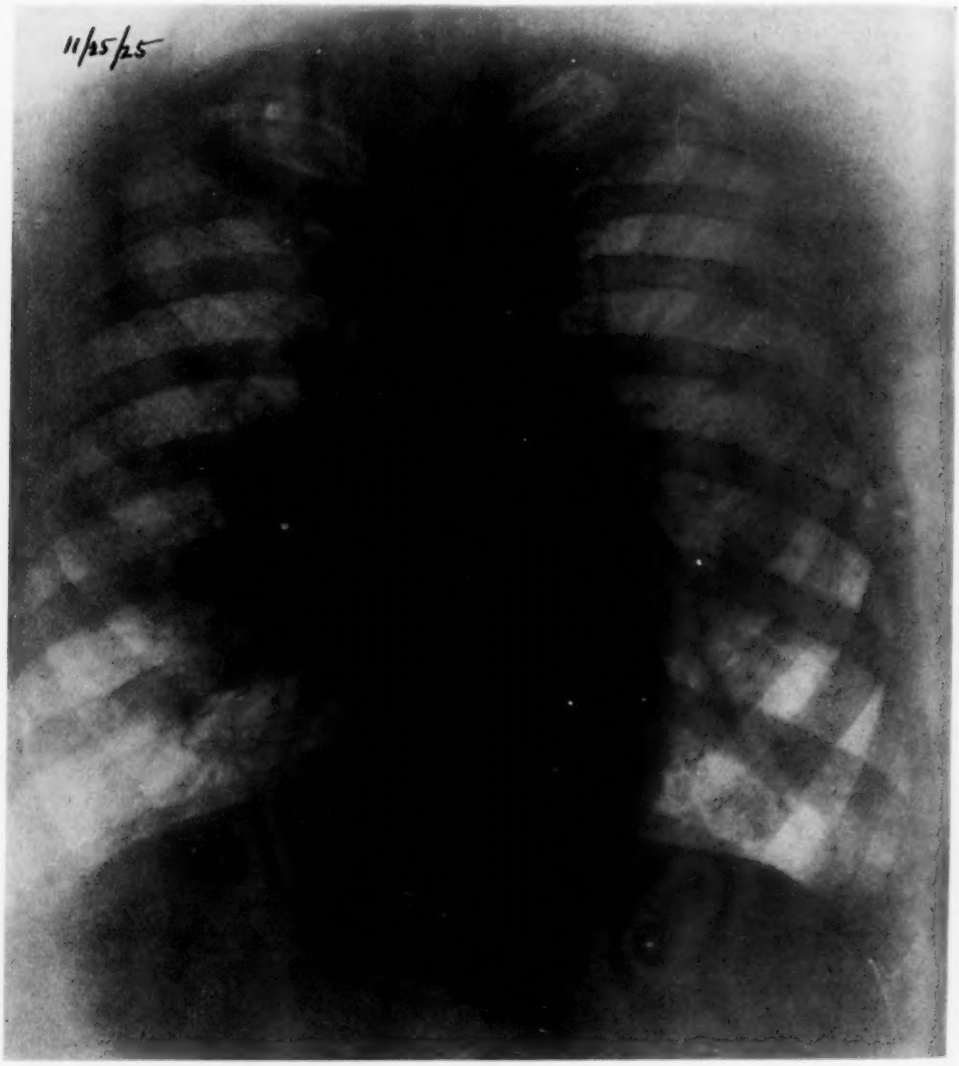


FIG. 1. Roentgen-ray of the chest taken in 1925 (seven years prior to admission). Note annular shadow in right hilic region.

was increased with deep inspiration and cough, and would persist for several weeks with remissions of several months. At this time, the patient was under the care of his family physician, at whose direction a roentgenogram was made (figure 1). This film shows near the right pulmonary hilus a rounded mass of even consistency unassociated with other parenchymal changes.

It was just at this time that the patient's father died of tabes, and that the patient himself was found to have a four plus Wassermann reaction. Anti-syphilitic treatment was carried on for one year. While his Wassermann reaction never became negative, a roentgenogram of the chest one year later (figure 2) shows the dis-

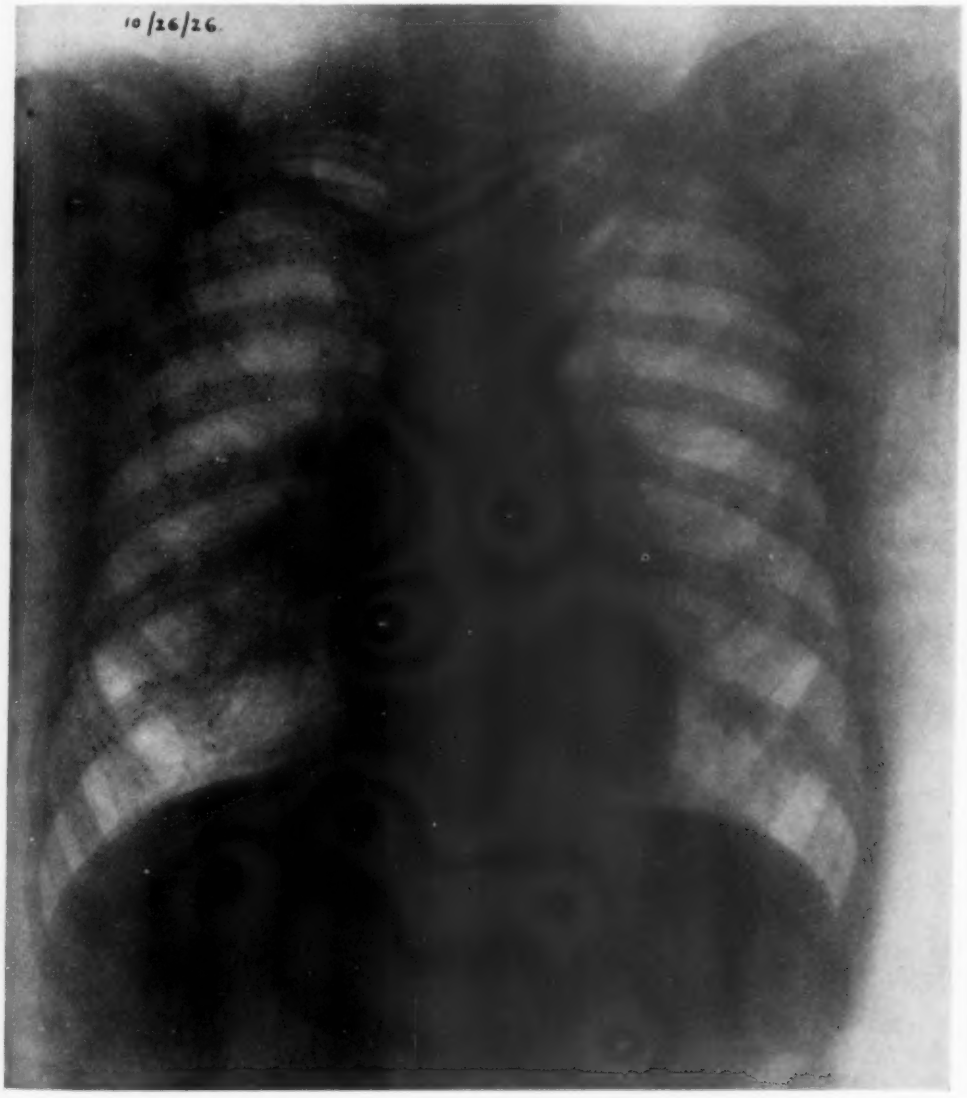


FIG. 2. Roentgen-ray of chest one year later. Note annular shadow is replaced by increase in fibrous tissue structure.

appearance of the annular shadow with marked increase in the fibrous structure of the right lower lobe. On admission to the hospital (seven years after the original plate) the changes in the right lower lobe are even more striking, with tremendous increase in the fibrotic changes. (Figure 3.)

In his gastrointestinal history, one incident that occurred nine years before de-

serves comment. At that time he says that everything he swallowed caused excruciating pain in the right upper quadrant near the midline. This sensation lasted about 10 days and disappeared entirely. Two months prior to admission the patient himself noticed an abdominal mass, but he was quite unconcerned about it.

He was admitted to the hospital after having been apprehended while in the act

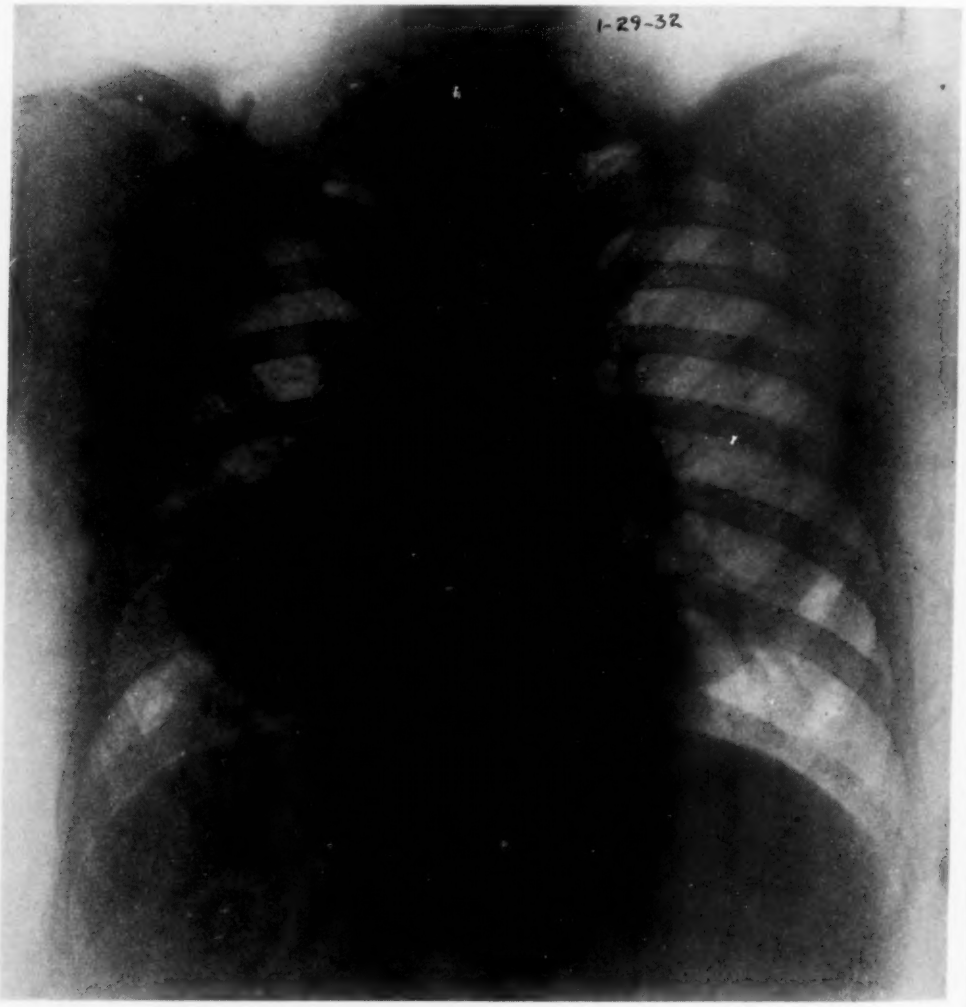


FIG. 3. Roentgen-ray of chest taken on admission seven years after figure 1. Note fibrous tissue proliferation in right hilic region, more marked than in figure 2.

of walking off a wharf. He claimed there was no suicidal intent, that everything seemed clouded and that he just could not stop himself. This incident was responsible for his hospitalization.

The physical examination revealed the following positive findings. In the chest over the right lower lobe there was increased tactile fremitus, impairment of the percussion note, and broncho-vesicular breathing with persistent fine râles.

The abdomen revealed a large firm mass which extended diagonally from above the costal margin on the left, downward and to the right. Its lowest border was 3.5 cm. below, and 1.5 cm. to the right of the umbilicus. A deep notch could be felt on its

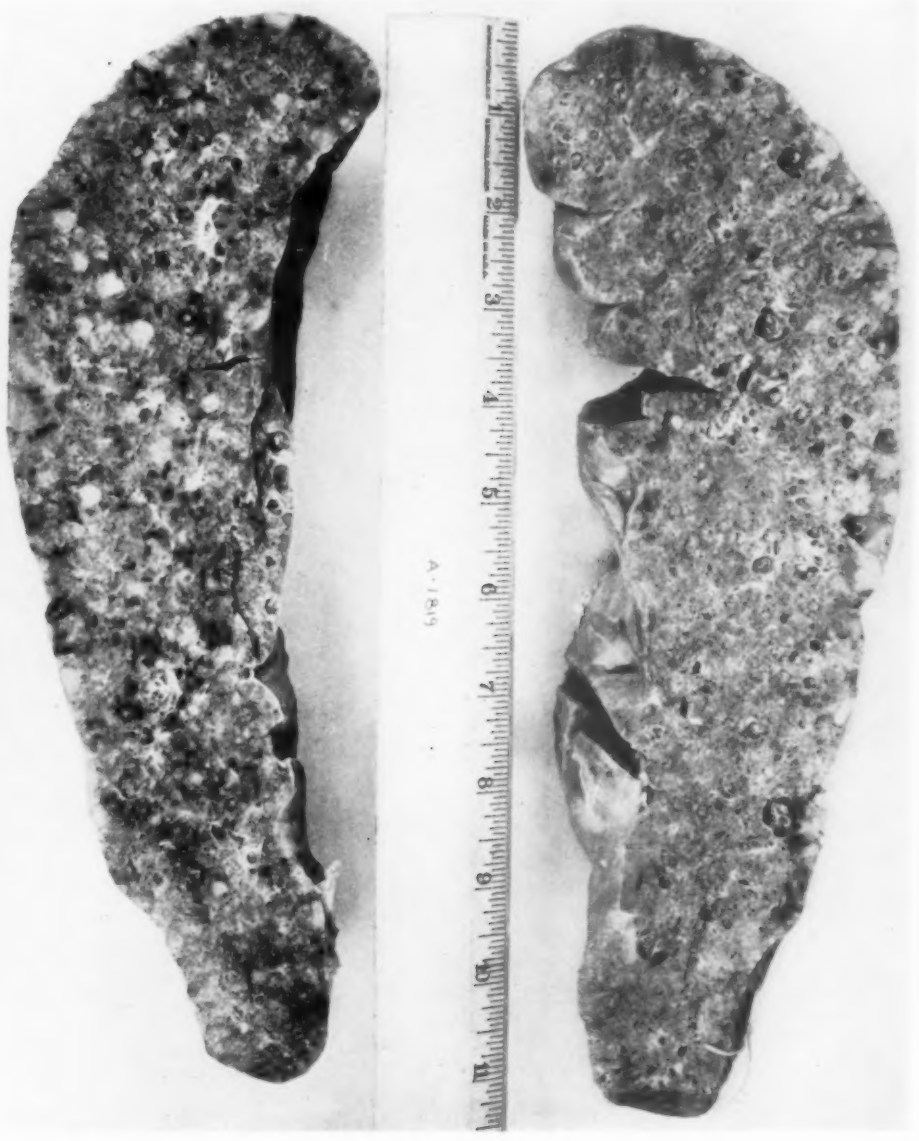


FIG. 4. Spleen—sectioned.

right border. It was freely movable but did not move with respirations. A roentgen-ray after pneumo-peritoneum revealed a very striking picture of this mass which was believed to be the spleen.

In addition there was a marked clubbing of the fingers but otherwise the physical and neurological examinations were not remarkable. The pulse rate, temperature and respirations were normal.

A considerable amount of laboratory work was done, including numerous blood counts, platelet counts, blood chemistry determinations, renal function tests, liver function tests, fragility test, and gastric analysis. All these were normal. The sputum persistently showed gross and microscopic blood, but repeated examinations revealed no fungi, spirochetes or tubercle bacilli. The Wassermann reaction of the blood was four plus; that of his spinal fluid was negative.

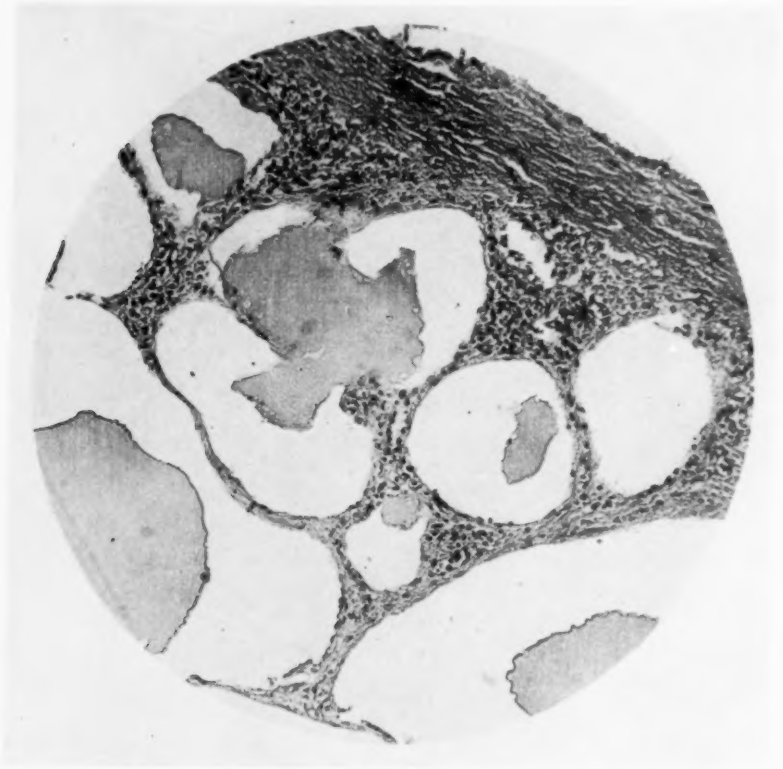


FIG. 5. Microphotograph of spleen (high power).

One month after his admission, the patient was examined bronchoscopically. This procedure was attended by considerable bleeding, and shortly thereafter he developed what was obviously a lung abscess. During a violent coughing attack two months later, he died. During his stay in the hospital, stringent anti-syphilitic treatment had been given.

The clinical diagnosis was (1) syphilis of the lung, (2) amyloidosis or multiple gummata of the spleen, and (3) lung abscess. An autopsy was performed three hours after his death and the complete protocol is appended herewith.

The body was that of a fairly well developed, poorly nourished white male in early middle life. The skin showed no striking abnormalities anywhere. The pupils were round and equal, and moderately contracted. The nasal septum was intact. The buccal mucous membranes and the teeth were not remarkable. The genitalia were

normal. There was marked clubbing of the fingers and loss of the nail on the right forefinger.

The body was opened in the usual manner, and considerable subcutaneous emphysema was noted. The peritoneal surfaces were smooth and glistening. The spleen, which will be described in detail later, extended beyond the midline to the right side, diagonally across the abdominal cavity, so that it terminated about 4 cm. to the right and 4 cm. below the umbilicus. The liver was about three fingers-breadth below the

FIG. 6. Cross specimen of lung (sectioned). Note: left lung is entirely normal.

costal margin. Otherwise the arrangement and color of the organs appeared normal. The left pleural cavity presented no adhesions and contained no fluid. The right pleural cavity, however, was abnormal. The pleural surfaces were in places bound down together. The lung was removed together with the pleural cavity by stripping the parietal pleura from the chest wall. About a liter of pus was removed from the anterior portion of this pleural cavity. Laterally and posteriorly the pleural surfaces were firmly bound down together, thereby obliterating completely the pleural space.

The pericardial cavity was everywhere smooth and glistening. There were no pericardial adhesions and no excess of fluid.

The *heart* weighed 300 gm. The valve measurements were: tricuspid, 12.5 cm., pulmonic, 7.5 cm., mitral, 8.5 cm., and aortic, 6 cm.

The heart was essentially of normal size. The epicardial surface was, in places, somewhat thickened. It had a dull grayish appearance, but there was no exudate. There was no atrophic change in the sub-epicardial fat and the surface vessels were not tortuous. The myocardium was not remarkable. When first sectioned there were some areas that looked like fresh scarring, but these were not evident later. The endocardium was normal. The mitral valve was entirely normal. The aortic valve revealed a few fenestrations but it was otherwise smooth and delicate. The tricuspid and pulmonic valves were normal. The openings of the coronary arteries were patent and the arteries themselves were smooth and delicate. In the pulmonary artery and just above the anterior leaflet of the pulmonic valve there was a small cyst. This was perfectly clear and measured about 1 mm. in diameter.

FIG. 7. Microphotograph of right lung.

The pleural surface of the *left lung* was perfectly smooth and delicate, and on section the lung was entirely normal. There were no areas of consolidation and no cysts were seen in this lung. However, one of the bronchial nodes on this side contained calcified tubercles and another one just above it was entirely cystic and contained a clear greenish yellow fluid.

The *right lung*, however, was strikingly abnormal. It was moderately increased in size and the visceral and parietal pleurae were bound together posteriorly. Anteriorly was the empyema cavity, previously described. On cut section between the visceral and parietal pleurae, were a large number of multilocular cysts. These measured between 1 mm. and 1 cm. in diameter; some were hemorrhagic, while others contained a greenish yellow coagulated substance. The upper lobe of this lung was air-containing and apparently of normal color. The lower lobe was unusual. Posteriorly, extending from the bronchus, a small abscess cavity was seen. It was lined with exudate and from it, extending anteriorly and piercing both visceral and parietal pleurae, extended an opening somewhat less than 1 cm. in diameter. That this must

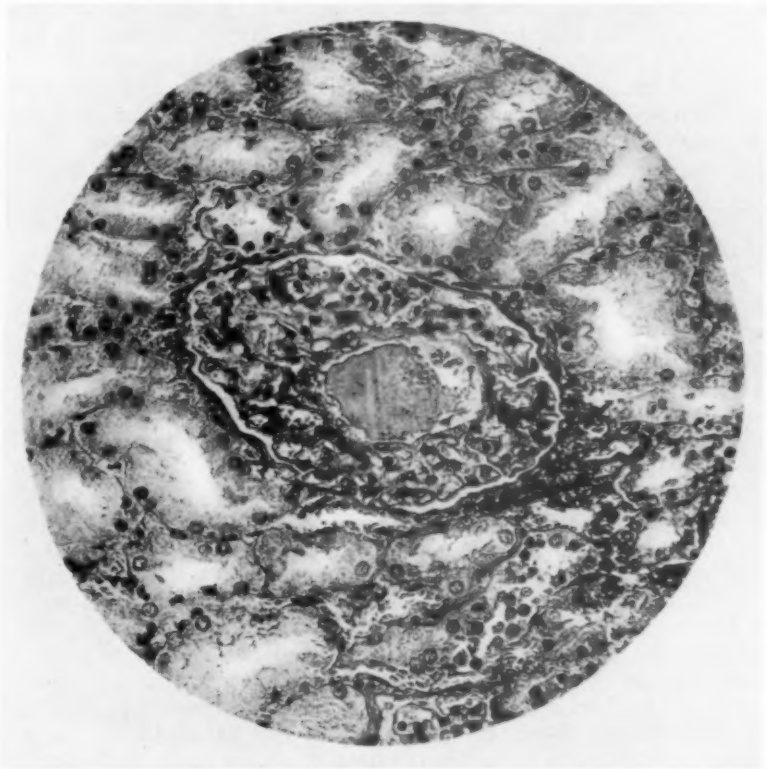


FIG. 8. Microphotograph of kidney showing a cyst in one of the glomeruli. This contains clear colloid.

have existed in this fashion for some time was obvious, because both layers of pleurae were fused together about this opening and the entire tract that had been so produced was lined with a shaggy exudate.

Anteriorly, in the lower lobe, were the following changes. Along the mediastinal border there was a round lobulated mass which measured 4 cm. across its greatest diameter. On section this contained within it many yellowish caseous looking necrotic areas, and extending into it from the outside were bands of scar tissue. This area was extremely vascular. By another section made 2 cm. posteriorly this cavity was reduced to a diameter of 2 cm. Beyond this were seen many cysts, most of which were near or around the blood vessels. The smallest measured about 1 or 2 mm. in

diameter, while the largest one within the lung measured 1.5 cm. in diameter. Most of them were blood tinged; many contain organized thrombi, while a few contained a perfectly clear, yellow, mucoid appearing, coagulated material. The entire lower lobe contained a brownish golden pigment quite like hemosiderin, and no such pigment was seen at all in the upper lobe. About the hilus of the lung and diminishing toward the parenchyma was a considerable amount of scar tissue. In the interlobar septum between the upper and lower lobes, two large cysts were observed. Practically every bronchial and mediastinal lymph node was involved in the same cystic degeneration and all contained the material just described, with the exception of two which, in addition, contained some yellowish caseous or necrotic-looking material. The middle lobe could not be found in this lung.

The *liver* weighed 2 kg. and measured 25 by 19 by 9 cm. It appeared moderately increased in size. The capsule was smooth and delicate, but beneath it, particularly over the right lobe, were myriads of angiomata which varied from pin point to 3 mm. in size. On the cut surface only one such nodule was seen within the depth of the liver itself. There was in places a suggestion of increase in fibrous tissue, but on the whole the liver appeared quite normal.

The *spleen* weighed 2100 gm. and measured 31 by 21 by 10 cm. Its enlargement was remarkable. Externally, the capsule was not increased in thickness and there was only one adhesion between the spleen and the lateral abdominal wall. The surface was roughened and myriads of cysts could be seen peering through it. On cut section there was nothing to be recognized as normal spleen. The entire organ was a cystic mass which simulated closely the above described changes in the lung—namely cysts (*a*) containing greenish yellow, clear, coagulated fluid. (*b*) Those containing organized thrombi. (*c*) Many blood tinged. (*d*) An occasional one containing necrotic or caseous looking material. These cysts were separated one from the other by a dense grayish yellow fibrous tissue stroma. Only a few blood vessels could be identified as such and their walls were moderately thickened. On cut section the surface suggested a slab of granite marble.

The *pancreas* was not remarkable. The peripancreatic lymph nodes are involved in the same general process.

The *kidneys* were of normal size. The capsules stripped easily. On the surface of both kidneys, however, many small hemangiomata similar to those described on the surface of the liver were seen. On cut surface the right kidney had a peculiar mottled appearance. However, the cortex was everywhere of normal width, and the striations were entirely regular. The pelves were not dilated. The ureters were normal. The bladder was normal. The right kidney weighed 200 gm. and measured 12.5 by 7 by 3 cm. The left kidney weighed 220 gm. and measured 14 by 7 by 3 cm.

The *pre-aortic* and *mesenteric lymph nodes* were likewise involved in the same cystic process. Nothing abnormal was noted in the *stomach, gastrointestinal tract, prostate gland, seminal vesicles,* or *aorta.*

On microscopic examination the *heart* seemed entirely normal and in two sections there was no evidence of any pathological change. The myocardium presented no scarring as mentioned above. The capsule of the *liver* was normal, and most of the liver cells appeared in a good state of preservation. There were no areas of necrosis and there was no amyloid. Many cysts were seen in these sections. Some of them were perfectly clear. Several contained fresh blood and one in particular contained both blood and a clear colloidal substance which stained pink and was probably serum. Most of these cysts appeared along the periphery of the organ and just under or in continuation with the capsule. A few, however, were seen deeper in the liver substance. These cysts in their proliferation seem to have followed several of the portal spaces. They were usually round or oval and many showed a definite endothelial lining. About several of them a moderate lymphocytic reaction could be seen.

The *spleen* was not recognizable as such. No Malpighian bodies could be seen, and the normal splenic pulp was completely replaced. One saw only myriads of cysts shrouded in a dense connective tissue stroma which had some lymphocytes scattered throughout. The endothelial lining could be seen in most of these cysts, and the vast majority contained colloid. Some contained fresh blood and in at least one an organized thrombus was found. In places, it seemed as if the fibrous tissue trabeculae of the stroma were extending into the cysts themselves.

In the *kidney,* most of the glomerular and tubular tissue appeared normal. However, many cysts were found in this organ as well. These were essentially of the same type as described but were found within the glomeruli themselves. Most of them were filled with colloid and red blood cells and under high power were seen to have an endothelial lining made up of only two or three cells, but even in this minute state some seem to be multilocular. Other large cysts or hemangiomata were found in the interstitial tissue between the tubules and approached the size of those seen in the liver.

The *adrenals* were essentially normal except that in a single section two cysts were found.

The *pancreas* was normal except for a few microscopic, colloid-bearing cysts

One section of a *lymph node* revealed the replacement of the normal tissue by this cystic process.

The *left lung* was entirely normal. Many sections were taken from the *right lung* and the first studied was from the portion near the hilus where a considerable amount of dense scar tissue was seen grossly. This was borne out microscopically and within this dense scar tissue, many small cysts, some filled with blood, were seen. This was the area which corresponds to the mass seen by roentgen-ray in 1927, and the thick walls about the cysts in this area suggested that the process may have dated back to that time. The remainder of the section showed many small cysts and in addition necrotic abscess cavities undergoing liquefaction. There were many leukocytes in these cavities and polymorphonuclear cells predominated. About each of the smaller blood vessels, both in the scar tissue and the remainder of the lung spaces, a very striking ring of what seems to be elastic tissue could be seen, and that this was really elastic tissue was borne out by a Verhoff-Van-Giesen stain. One also saw many large phagocytic cells containing considerable blood pigment. The alveoli that remain are large, emphysematous in type, and with thinned-out friable walls. A stain for tubercle bacilli was entirely negative.

A second section was taken from the area described as spherical and containing caseous or necrotic areas. Microscopical examination revealed these to be small abscess cavities probably pyogenic in origin since most of the reaction was of the polymorphonuclear type. There was no well defined capsule about these abscesses and many of them were undergoing liquefaction in their centers. The spaces between these abscesses were filled with scar tissue and the vessels in this tissue also showed, though in lesser degree, a rim of elastic tissue. Such elastic tissue was found only about the smaller vessels and never about the cysts. Many small cysts were also seen in this section, and toward the periphery, larger and more typical hemangiomata were found. These larger cysts were all very well defined and each showed a definite lining of endothelial cells. In one area there was definite bone formation with marrow within it. Another area likewise showed bone formation but no marrow was observed. The position of this bone formation was peribronchial and it was considered to be an example of metaplasia. The bronchi in this section were full of exudate which was similar to that in the abscess cavities. A search for acid-fast bacilli revealed none. A third section from the base added nothing that has not been described previously.

A fourth section was taken from the periphery of the lower lobe in the mid-

portion at the axilla. From without inward it was seen that the parietal pleura and visceral pleura were both thickened and contained considerable granulation tissue which showed new sprouting capillaries throughout. These are extremely numerous and pervade the entire substance. Between these layers, one saw many cysts filled with colloid and lined with endothelium. Several cysts also contained blood, but none was found which contained thrombi.

The fifth section was taken from the trachea and included a peritracheal lymph node of the mediastinal group. It showed normal lymphoid tissue to have been completely replaced by cysts.

Anatomical Diagnosis. Histologically benign, metastasizing hemangiomata involving spleen, liver, kidneys, pancreas, adrenals, intima of the pulmonary artery, the right lung, the mesenteric, peripancreatic, pre-aortic and mediastinal lymph nodes. Pyogenic abscess in the lower lobe of the right lung; with a bronchopleural fistula, pyothorax and subcutaneous emphysema; moderate cardiac hypertrophy.

This unusual condition, clinically so misjudged because of the positive Wassermann reaction, was, at postmortem examination, accompanied by no evidence of syphilis. Other cases similar to ours have been reported in the literature since 1879 (Langhans) but in no instance have we been able to find another case in which a positive Wassermann reaction was present. It seems clear that there is no connection between these two conditions. The name, histologically non-malignant metastasizing hemangioma, was first used by Thomas Shennan in his report of a case. Other authors have called this condition "telangiectatic splenomegaly," "diffuse hemangioma," "malignant hemangioma," "obliterating angioma," etc.

Most of the reported cases do not show the widespread involvement observed in ours. On the other hand a few have revealed foci that were not involved in this case. In Shennan's case the spleen weighed 1510 gm. and there were cystic spaces in the sternum and clavicle. In Homans' case the omentum was involved. Theile reported cystic changes in the stomach.

In addition to these, many pathologically similar examples in which only the spleen is involved can be found in the literature. However, we do not believe that in any case thus far described have the changes been so widely diffused as in this one.

BIBLIOGRAPHY

1. Albrecht, H.: Ueber das Cavernom der Milz. Ein Beitrag zur Kenntnis von Bau und Entstehung der Cavernome, Ztschr. f. Heilk., 1902, xxiii, 97.
2. Anzilotti, G.: Sugli angiomi multipli della milza, Tumori, Roma, 1913–14, iii, 261.
3. Benckendorff, Elisabeth v.: Untersuchungen eines Angiomes der Milz, Virchow's Arch. f. path. Anat., 1908, cxciv, 500.
4. Borrmann, Robert: Zum Wachsthum und zur Nomenclatur der Blutgefässgeschwülste, Virchow's Arch. f. path. Anat., 1899, clvii, 297.
5. Homans, John: Report of a case of cavernous angioma of the spleen, Ann. Surg., 1897, xxv, 732.
6. Langhans, Theodor: Casuistische Beiträge zur Lehre von den Gefässgeschwülsten, Virchow's Arch. f. path. Anat., 1879, lxxv, 273.
7. Theile, Dr. med.: Über Angiome und sarkomatöse Angiome der Milz, 1904, clxxviii, 296.
8. Dowd, C. N.: Cavernous angioma of the spleen, Ann. Surg., 1915, lxii, 177.

9. Symmers, Douglas: Telangiectatic splenomegaly, Jr. Am. Med. Assoc., 1921, lxxvii, 2019.
10. Wright, A. W.: Primary malignant hemangioma of the spleen with multiple liver metastases, Am. Jr. Path., 1928, iv, 507.
11. Kellert, Ellis: Diffuse hemangioma of the spleen, Am. Jr. Cancer, 1932, xvi, 412.
12. Shennan, Theodore: Histologically non-malignant angioma, with numerous metastases, Jr. Path. and Bact., 1914–15, xix, 139.
13. Steiner, W. R.: Hereditary hemorrhagic telangiectasia, Nelson Loose Leaf Medicine, Volume IV (Diseases of blood, circulatory system, kidney), 162A.
14. Wollstein, Martha: Malignant hemangioma of the lung with multiple visceral foci. Report of a case, Arch. Path., 1931, xii, 562.

INFECTIOUS MONONUCLEOSIS COMPLICATING TYPHOID FEVER*

By Alfred S. Schwartz, M.D., and Bernard Lidman, M.D.,
Baltimore, Maryland

The simultaneous occurrence of typhoid fever and infectious mononucleosis has not previously been recorded in the literature. The case reported below is an instance of such coincidence.

Case Report

Dr. I. S., aged 25, a member of the house staff of this hospital, was admitted to the service of Dr. Charles R. Austrian on August 29, 1937, complaining of malaise and sore throat of three days' duration. Except for a history of asthma in the father and hay fever in one brother, the family history was negative. The patient had the usual diseases of childhood without sequelae and a tonsillectomy at the age of six. At 10 he had diphtheria and was treated with antitoxin. He had also had recurrent luxation of the right humerus and a right eustachian salpingitis for the previous five years. One year before admission, he had received only two of the recommended three injections of typhoid-paratyphoid combined vaccine (0.5 c.c. and 1.0 c.c., at an interval of one week).

Three days before admission the patient noted that his throat felt a little sore, but continued with his work. He suffered so little discomfort that the afternoon before admission he went swimming. A few hours later, he noticed a recurrence of his sore throat and felt alternately feverish and chilly. His temperature at this time was 101.5° F. Because of increasing malaise, the patient was admitted to the hospital on the following morning.

On admission, the temperature was 100° F., pulse 88, respirations 16. The patient was a tall, asthenic young man, somewhat underweight, who appeared to be moderately ill. The skin was warm and dry; there was no exanthem. No general or localized glandular enlargement was noted. The pupils were round, regular, equal, and reacted briskly to light and accommodation. There was no nasal discharge or inflammation of the nasal mucous membrane and although the pharynx and fauces showed a diffuse reddening, there was no exudate. Small tonsillar tags were seen. The thyroid gland was not enlarged. The lungs were clear except for a few transient sibilant rhonchi, and the heart was negative. The genitalia and extremities were nor-

* Received for publication May 18, 1938.
From the Department of Medicine, Sinai Hospital of Baltimore.

mal. The neurological examination revealed no abnormalities. The number of leukocytes on admission and subsequently are recorded in table 1. There was no anemia. Urinalysis was negative. The Wassermann reaction of the blood serum was negative. Throat cultures revealed a mixed growth of pneumococcus, staphylococcus, *Micrococcus catarrhalis*, and non-hemolytic streptococcus. No Klebs-Loeffler or Vincent's organisms could be demonstrated.

The temperature was remittent with a morning fall to around 100° F., and a rise to levels between 102° and 104.6° F. at night. The pulse rate ranged between 88–100 a minute during the febrile period. The posterior cervical lymph nodes became slightly enlarged shortly after admission. On September 1, the third day after admission and the seventh day after the onset, *Bacillus typhosus* was identified in culture from the blood and the same organism grew in numerous subsequent cultures of the urine and stools. Early in the course of the disease, the patient's chief complaints were nausea, anorexia, chilly sensations, and generalized malaise. A week after admission, he complained of an intensely severe sore throat which was much more pain-

TABLE I

Leukocyte Counts

Date	W.B.C. per cu. mm.	Juv. PMN %	PMN %	Lymph. %	Mono. %
8–29–37	5850	9	61	25	5
8–30–37	3300	30	42	23	5
8–30–37	3750	27	31	40	2
8–31–37	5000	34	19	37	10
9–1–37	4000	22	20	54	4
9–2–37	5350	13	32	52	3
9–3–37	5950	17	27	54	2
9–4–37	7900	16	20	64	0
9–5–37	8200	13	17	69	1
9–6–37	7400	14	12	74	0
9–7–37	16500	10	14	72	4
9–8–37	12700	14	12	67	7
9–9–37	10400	12	21	63	4
9–10–37	10750	14	25	51	10
9–11–37	10400	0	32	41	27
9–12–37	8550	6	24	57	13
9–15–37	6200	7	29	55	9
9–24–37	6050	0	33	62	5
9–29–37	5800	7	56	31	6

ful than the initial mild irritation. For the next 10 days, faucial pain was constant and severe. The mucous membrane of the fauces and pharynx continued to show a diffuse, dusky erythema, but no exudate developed. During this period a shallow ulcer, about 1 cm. in diameter, developed at the base of the right tonsillar fossa and although it persisted for two weeks in spite of local treatment, it did not increase in size. Repeated cultures of the oral cavity revealed no change in the flora. At the onset of this sore throat, the moderately firm, rounded edge of the spleen became palpable just below the costal margin, but there was no general enlargement of the peripheral lymph nodes at this or any other time during the course of the illness. There was no change in the size of the posterior cervical nodes. The tonsillar glands were a little enlarged and moderately tender.

Because of the severity of the pharyngeal manifestations, and because of the increasing leukocytosis with a marked preponderance of mononuclear elements, it was thought that infectious mononucleosis had developed. On September 9, a heterophile

antibody agglutination was positive in a dilution of 1:256 (table 2). On the following day, the monocytes of the blood rose to 10 per cent of the total white cell count, and two days later they constituted 27 per cent of the leukocytes (table 1). The temperature did not rise above normal limits on September 12, and from this time on the patient improved rapidly without further complications. Repeated cultures of the urine and stools were negative for *Bacillus typhosus* after the defervescence, and the patient was discharged cured on October 1.

TABLE II

Agglutination Reactions

	Agglutination Titer				
Date	9–1–37	9–5–37	9–9–37	9–15–37	10–15–37
Antigen					
B. typhosus	1 : 50	1 : 160	1 : 320	Not done	Not done
B. paratyphosus A	0	1 : 20	1 : 160	Not done	Not done
B. paratyphosus B	1 : 50	1 : 40	1 : 160	Not done	Not done
B. suipestifer	Not done	1 : 20	0	Not done	Not done
B. dysentery (polyvalent)	Not done	1 : 20	0	Not done	Not done
B. proteus X2 and X19	Not done	0	0	Not done	Not done
B. melitensis—bovine	Not done	0	0	Not done	Not done
porcine	Not done	0	0	Not done	Not done
caprine	Not done	0	0	Not done	Not done
Sheep cells	Not done	Not done	1 : 256	1 : 128	1 : 64

COMMENT

The diagnostic problem of differentiating between typhoid fever and infectious mononucleosis arises not infrequently. Malaise, headache, epistaxis, slight sore throat, fever and relative bradycardia are early manifestations encountered commonly in both diseases. It is of interest that both these diagnoses were suggested early in the course of this case. The demonstration of *Bacillus typhosus* in cultures of the blood, of the urine, and of the stools and the increasing titer of the Widal reaction established the diagnosis of typhoid fever.

Suspicion that an unusual complication might be present was aroused because of the prominence of the pharyngeal manifestations associated with the sudden rise of the leukocytes to 16,500 per cu. mm., 76 per cent of which were mononuclear cells. In his analysis of 829 cases of typhoid fever treated at the Johns Hopkins Hospital during the first 10 years of its existence, Osler [3] found only five cases in which the pharyngitis was sufficiently severe to cause annoyance and require local treatment. In Thayer's [2] investigations of the blood counts found in this same series, there is no record in which the percentage of polymorphonuclear cells fell to such low levels in the presence of so marked a leukocytosis. The demonstration in the patient's blood serum of agglutinins for sheep cells in a dilution of 1:256 in the absence of any recent administration of horse serum, indicated clearly that infectious mononucleosis complicated the primary disease. Although Bernstein [1] demonstrated the presence of bacterial agglutinins in a number of cases of infectious mononucleosis, he found no increase of the agglutinins for sheep erythrocytes in the serum of a series of pa-

tients with typhoid fever. The subsequent appearance of an increase in the number of atypical monocytes to 27 per cent of the total leukocyte count, confirmed the clinical and serological findings.

Although it is obvious that the two injections of combined typhoid-paratyphoid vaccine administered in 1936 failed to immunize the patient adequately, it may be that the severity of the typhoid infection was ameliorated thereby, as the febrile period lasted only 17 days despite the presence of an unusual complication.

Summary

A case of typhoid fever complicated by infectious mononucleosis is presented.

REFERENCES

1. Bernstein, A.: Antibody responses in infectious mononucleosis, Jr. Clin. Invest., 1934, xiii, 419.
2. Thayer, W. S.: Studies in typhoid fever, 1901, The Johns Hopkins Press, Baltimore, iii, 489.
3. Osler, W.: *ibid.*, iii, 457.

EDITORIAL

OBSCURE FORMS OF SUBACUTE COR PULMONALE

During recent years in which clinicians in the United States have become interested in the syndrome of right heart failure, the causes of increased resistance to the pulmonary circulation have been restudied. The problem is a fascinating one because we possess as yet no direct method of measuring the pressures in the pulmonic arteries or veins and must proceed largely through indirect means.

Our basic information we owe to the postmortem observations of disproportionate hypertrophy and dilatation of the right ventricle in certain lesions of the lungs which would apparently entail a diminution in the pulmonary vascular bed; for example, in extensive pulmonary fibrotic processes, in extreme kypho-scoliosis with disproportionately small lungs, in massive types of silicosis, and occasionally in high grades of emphysema. It has become evident in the study of such pulmonary lesions that it is only diffuse lesions which can cut down the cross section of the pulmonary blood flow sufficiently to cause a heightened resistance to the normal output of the right ventricle. We know, for instance, that total collapse of one lung or, indeed, the removal of one lung can be compensated by the full utilization of the vascular bed of the remaining lung without apparent strain upon the right heart.

Such diffuse pulmonary lesions as have been mentioned are usually detectable by clinical methods of examination. The development of right heart failure in these may often be followed from the early stage in which it is doubtful whether the dyspnea present is chiefly pulmonary or chiefly circulatory to the time when engorged jugulars, enlarged liver and edema of dependent parts indicate plainly the congestion secondary to failure of the right ventricle.

Far less easy to interpret clinically are certain cases of dyspnea and cyanosis of subacute type, apparently of circulatory origin, in which the only abnormalities discoverable by physical examination, roentgenography and electrocardiography are evidences of dilatation of the pulmonary conus and main pulmonary arteries, accentuated second pulmonic sound, and right axis deviation. These indicate pulmonary arterial hypertension and right ventricular hypertrophy, but the nature of the increased resistance in the pulmonary circuit remains unrevealed.

There are at least three conditions which may give rise to such a clinical picture: (1) primary pulmonary arteriosclerosis; (2) pulmonary arteritis; and (3) lymphangitic carcinomatosis of the lungs.

If the strict criteria set up by Steinberg are followed, the condition known as primary pulmonary arteriosclerosis is a very rare one. Steinberg advised the restriction of the term to those cases in which there was absence of all

lesions known to produce pulmonary arteriosclerosis as a secondary consequence. This would exclude cases showing mitral stenosis, congenital cardiac and vascular anomalies with communication between the systemic and pulmonic circulations, congenital narrowing of the pulmonary veins, outspoken emphysema, diffuse pulmonary fibroses and extensive pleural adhesions. In addition, it should be noted that Brenner [1] has shown that moderate grades of pulmonary arteriosclerosis are very frequently found without any evidence at autopsy of right ventricular hypertrophy or clinical history suggesting right heart failure. There remain, however, instances in which right heart failure was present in life without obvious explanation, and in which careful postmortem studies disclosed as the sole apparent cause extensive sclerosis in the small arteries and arterioles of the lungs. The microscopic details of the arterial lesions are in no way specific. In certain reported cases marked intimal proliferation had led to partial or complete occlusion of the vessels, while in other cases the media was more prominently involved. In one of Brenner's cases with marked hypertrophy and dilatation of the right heart no pathogenic factor other than the pulmonary arteriosclerosis was found, but the extent of the arterial change present seemed no greater than this author had observed in other cases presenting no evidence of right heart strain. It has been suggested that such cases are explainable by the occasional occurrence of an essential pulmonary hypertension due to vasoconstriction, analogous to essential hypertension in the systemic circulation, and that the changes in the smaller pulmonary vessels and in the right ventricle occur only as a secondary effect. Direct evidence for the validity of such a conception is lacking.

In certain instances the clinical picture of subacute or chronic right heart failure may develop as a result of diffuse arteritis or thromboarteritis of the pulmonary arteries. In the majority of cases of arteritis, however, whether or not associated with thrombosis, clinical and pathological evidences do not indicate that pulmonary hypertension had existed in life.[2]

A specific form of arteritis due to syphilis, and accompanied by chronic right heart failure, polycythemia and marked cyanosis, has been described by several authors and is usually given the name of Ayerza's disease. The reported cases have been reviewed by Brenner who concludes that the proof of the syphilitic nature of the arterial lesions is in almost all of these cases quite unconvincing. Syphilis of the pulmonary aorta and large pulmonary arteries has been established in a number of cases,[3] most of which, however, presented no evidence of pulmonary hypertension. It seems probable that syphilis of the small arteries and arterioles with consequent right heart over-

[1] BRENNER, O.: Pathology of the vessels of the pulmonary circulation. Part IV, Arch. Int. Med., 1935, lvi, 976.

[2] BRENNER, O.: Pathology of the vessels of the pulmonary circulation. Part V, Arch. Int. Med., 1935, lvi, 1189.

[3] KARSNER, HOWARD T.: Sclerosis of the pulmonary arteries, Chapter XVI in "Arteriosclerosis" (edited by EDMUND V. COWDRY, PH.D.), 1933, The Macmillan Company, New York, p. 457.

load is extremely rare, and that many of the cases in which it was suspected are examples of primary or secondary pulmonary arteriosclerosis.

Rheumatic pulmonary arteritis, diffusely involving the arterial tree in the lungs, has been accepted as an entity, but data are not available as to the effect on the pressure in the pulmonary arterial circulation.

In septic states minor embolisms of the lesser branches of the pulmonary arteries are probably far more frequent than is commonly realized. Under certain conditions such emboli become organized with partial or complete occlusion of pulmonary vessels. Occasionally secondary arteritis with propagating thrombi may occur. There are also non-embolic forms of pulmonary arteritis occurring in septic states, and over such areas of arteritis occluding thrombi may form.[4] Occasionally in this whole group of cases, an instance is observed in which the typical picture of right heart failure has supervened.

The third category of cases mentioned included those in which pulmonary hypertension resulted from lymphangitic carcinomatosis of the lungs.[5] Clinically these cases are only rarely diagnosed, since they tend to occur before the usual age for carcinoma, and the primary growth which is usually in the stomach has a striking tendency to be symptomatically latent. In the forefront of the clinical picture stands an unexplained increasing dyspnea with evidences of right heart strain. The pulmonary physical signs are slight or absent, and no gross changes in the lungs are found in the roentgenogram. A fine reticular pattern in the lung parenchyma has been described as a helpful sign. The course is rapidly downhill with increasing tachypnea and asphyxial episodes.

Autopsy reveals the primary tumor which is often a flat diffusely infiltrating scirrhous gastric carcinoma, but may be situated in other organs. The gross appearance of the lungs may be normal, but often the subpleural lymphatics show as a white network. Microscopically the perivascular and peribronchial lymphatics are distended with tumor cells. In addition, the lesser arteries are frequently plugged with tumor thrombi in various stages of organization. The smaller arteries show a widespread sclerosis with partial or complete obliteration of their lumens. It is assumed that this latter change is due to a toxic effect of the adjacent tumor growth in the perivascular lymphatics. The right ventricle is usually dilated and may also show marked muscular hypertrophy of its wall. While the mechanism of this type of tumor dissemination is still far from clear, the condition itself is a relatively well defined entity and should be remembered in the study of any case of obscure dyspnea with unexplained right heart failure.

M. C. P.

[4] Fowler, W. M.: Obliterating thrombosis of the pulmonary arteries, Ann. Int. Med., 1934, vii, 1101.

[5] Jarcho, Saul: Diffusely infiltrative carcinoma. A hitherto undescribed correlation of several varieties of tumor metastasis, Arch. Path., 1936, xxii, 674.

REVIEWS

Diagnosis and Management of Diseases of the Biliary Tract. By R. Franklin Carter, M.D., F.A.C.S.; Carl H. Greene, Ph.D., M.D., F.A.C.P.; John Russell Twiss, M.D., F.A.C.P. 432 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1939. Price, $6.50.

The authors have written an interesting book based in large part upon the data accumulated during the past 20 years in the special clinic for diseases of the liver and biliary passages which is a part of the New York Post-Graduate Medical School and Hospital. The relatively uniform use over considerable periods of a routine of investigation and of management of cases falling in this group adds to the value of such data. The authors, as a result of their study, have arrived at a definite point of view concerning many controversial topics.

There is an adequate discussion of the difficult subject of biliary dyskinesia and deductions are drawn as to the proper clinical management in individual instances. Other chapters contain procedures for duodenal drainage, hepatic function tests and biochemical methods of investigation. The entire subject of gall-bladder infection is fully dealt with both from the laboratory and clinical standpoints.

The whole latter section of the volume is devoted to the operative experiences of the clinic, and the conclusions derived seem to be in accord with the general trend of thought. There are added to nearly every chapter good bibliographies which add greatly to the value of the book.

The chief criticism is the large amount of repetition. In addition, some of the very recent contributions, such as the use of vitamin K in jaundice, are incompletely presented.

On the whole the subject is handled very well, and the volume is one that should be read by anyone interested in gastroenterology.

F. G. D.

The Physiology of Anesthesia. By Henry K. Beecher, A.B., A.M., M.D. 388 pages; 24 × 16 cm. Oxford University Press, New York City. 1938. Price, $3.75.

The author has presented the physiology of the anesthetic drugs in a clear, concise way. The numerous theories of narcosis are given in detail. The general action of anesthetics, as well as their effects on various systems of the body, are dealt with. It is a treatise which will be read with profit both by anesthetists and by internists.

T. R. A.

Laboratory Manual of the Massachusetts General Hospital. By Francis T. Hunter, M.D. 119 pages; 18 × 12.5 cm. Lea and Febiger, Philadelphia. 1939. Price, $1.75.

The author preserves in the revised edition the purpose and scope of the original manual. The book continues to be an excellent pocket reference for medical students, internes and practising physicians, containing only diagnostic and therapeutic procedures of proved value which have been systematically arranged and briefly written.

E. F. C.

Play Therapy in Childhood. By C. H. Rogerson, M.D., M.R.C.P., D.P.M. 64 pages; 21.5 × 14 cm. Oxford University Press, New York City. 1939. Price, $1.25.

This book is a short, very readable treatise on a recent and most promising technic in the psychiatric treatment of problem children. The author presents a study of 36

rather severe cases treated by this method. He describes four of these cases in some detail, and his general conclusions are based on the findings of the larger group. In the first chapter he gives the history of the development of this technic and discusses the literature. Throughout the book the author shows a sane, common sense approach to a topic that is confused by theoretical controversies. The book is indispensable to pediatricians who wish to study psychiatric and child guidance methods. It is also recommended to any physician who would appreciate a short, clearly written, well illustrated description of what takes place when a psychiatrist treats a problem child.

H. W. N.

Personality Development and Social Control in Terms of Constitution and Culture. By IRA S. WILE, M.S., M.D. 57 pages; 21.5 × 14 cm. Oxford University Press, London. 1939. Price, $1.25.

This little volume represents three lectures delivered at The Tavistock Clinic by Dr. Wile in July, 1937. The first, dealing with "Personality in Terms of Constitution," is a thoughtful consideration of the processes of structural change, which Dr. Wile winds up by saying: "If society is unable to make the needed adjustments in its external world, then the constitution is affected in a manner that stimulates it to attempt an adaptation of personality potentials to the demands of the situation." The second lecture is entitled "Personality in Relation to Culture." "It is obvious, therefore, that personality involves the mobilization of forces from within itself to meet specific cultural needs," including economics, personal rights and rights of others, sexual customs, religious and educational patterns. Of all this, Dr. Wile may be summarized in his own words: "Man is a microcosm in a macrocosm. He is an atom in a universe which exists only because there are atoms. But the relations of the atom are determined by the existence of the pressures of the universe. Man is thus a creator or a moulder of his world and at the same time a part of creation constantly moulded by the patterns in his multiple spheres of activity." The third lecture, "Social Control and the Prevention of Personality Disorders," is considerably longer than the other two. After recognizing the individual aspects, he goes into prevention of personality disorders as a social problem primarily referable to the community or to the nation. He reviews familiar facts of the economic waste of these illnesses, both in terms of the direct cost of the maintenance of the afflicted individual, and in terms of the frequently life-long drain upon the community's resources entailed by the loss of the services of these patients, many of whom are potentially fine minds, cut off in youth or early adult age. He makes some general suggestions as to social factors including various governmental security acts which may do something to contribute to the surety with which the individual develops.

H. M. M.

COLLEGE NEWS NOTES

A. C. P. Committees and Board of Regents to Meet

The regular autumn meetings of the various special Committees of the College and of the Board of Regents will be held at the College Headquarters in Philadelphia, December 16–17. Matters for consideration and action include the review of the credentials of more than two hundred candidates for Associateship and Fellowship, the presentation of the program for the Twenty-fourth Annual Session to be held in Cleveland, April 1–5, 1940, the consideration of amendments to the Constitution and By-Laws, the presentation and adoption of a program of postgraduate courses for 1940, reports on future policies and many routine matters.

Proposal of Candidates

Attention of Fellows is called to the provisions of the By-Laws whereby proposals of candidates must be filed in the Executive Office of the College, 4200 Pine Street, Philadelphia, at least thirty days in advance of action. Meetings of the Committee on Credentials are scheduled for the following dates:

December 16, 1939
February 25, 1940
March 31, 1940

Gifts to the College Library

An act of courtesy and thoughtfulness, the presentation of his autographed book to the American College of Physicians by one of its Fellows, was the inspiration for the founding of a library of books of which members of the College are the authors. The Library, in a sense, is a memorial library to our members. A general medical library, other than one of this character, would scarcely be justified at the College Headquarters due to the availability of so many general medical libraries in Philadelphia. However, the type of collection now well begun is quite different, and will have a growing interest, an increasing value and a deeper sentiment as the years pass by. Already several hundred books have been received; a considerable number of the authors, early members of the College, are now deceased, but these copies of their books remain, memorials to those men in the College Headquarters.

The following recent contributions are gratefully acknowledged:

Book

Dr. Robert T. Monroe (Associate), Boston, Mass.—"Chronic Arthritis."

Reprints

Dr. Leila E. Andrews, F.A.C.P., Oklahoma City, Okla.—1 reprint;
Dr. Andrew L. Banyai (Associate), Wauwatosa, Wis.—20 reprints;
Dr. J. E. Greenstein, F.A.C.P., Providence, R. I.—1 reprint (in triplicate);
Dr. A. J. Logie (Associate), Jacksonville, Fla.—2 reprints;
Dr. Louis B. Owens (Associate), Cincinnati, Ohio—1 reprint;
Dr. Edw. C. Reifenstein, Jr. (Associate), Syracuse, N. Y.—11 reprints;

Dr. Ramon M. Suarez, F.A.C.P., San Juan, P. R.—2 reprints;
Dr. August A. Werner, F.A.C.P., St. Louis, Mo.—2 reprints.

The 1939 Directory of the College

The new and revised Directory of the College has been completed and mailed to every member of the College in good standing in his dues. In addition, about two hundred copies were sent gratis to the leading medical schools, medical societies and medical institutions of the United States and Canada. The Directory has become widely used as an index to competent physicians both by members and these institutions. The Directory is never sold to commercial firms or for commercial purposes.

This Directory contains the names and biographical data of 4,204 physicians, including 1 Master, 2,969 Fellows and 1,234 Associates, comprising the full College Membership. The following analysis of the specialty listings of members reveals an increasing number of admissions to the College of doctors engaged in the allied and related specialties, such as neurology, psychiatry, pathology, pediatrics, radiology, student and public health, and dermatology and syphilology. It may be noted by the reader that there are a limited few who have indicated their primary interest in the surgical specialties, but it should be explained that these members are not new acquisitions but members of early standing in the College when the surgical specialties were not so strictly excluded, or men who in later years turned from their original medical specialties to surgical specialties.

Specialty Analysis of the 1939 Directory

	Primary Specialty	Secondary Specialty
Internal Medicine	2740	34
Allergy	11	128
Arthritis	5	54
Aviation Medicine and Military Medicine	8	15
Cardiology	54	547
Communicable Diseases	1	3
Diagnosis	3	20
Diseases of the Chest	48	174
Endocrinology	10	66
Gastro-enterology	40	256
Hematology and Blood Diseases		21
Immunology and Preventive Medicine	5	14
Medical Education and Administration	21	31
Metabolic Diseases	13	138
Nutrition		2
Parasitology		1
Physical Therapy		19
Research	2	56
Tropical Medicine	5	28
Tuberculosis	70	116
Total Sub-specialties	296	1689
Total, Internal Medicine	3036	1723
General Medicine	277	12
Neurology and Psychiatry	206	73
Pathology and Clinical Pathology	169	120
Pediatrics	147	30
Radiology and Roentgenology	104	23
Public Health, Student Health	58	29
Dermatology, Syphilology	41	44
Surgical Specialties	12	9

MISCELLANEOUS				
Anatomy	2			
Bacteriology	12		20	
Biological Chemistry	2		2	
Cancer	1		1	
Industrial Medicine	11		11	
Legal-Cultural Medicine			2	
Life Insurance Medicine	2		1	
Medical Editing	1			
Pharmacology	5		2	
Physiology	7		1	
Retired	111			
		154		40
NO SECONDARY SPECIALTY GIVEN				2101
		4204		4204

REGIONAL MEETING, NORTH CAROLINA

Under the Governorship of Dr. Charles Hartwell Cocke, Fellows and Associates of the College for the State of North Carolina held their regional meeting at the University of North Carolina, Chapel Hill, Friday, October 20, 1939. They were also invited to attend the Postgraduate Symposium on "Diseases of the Lungs and Thorax" at Duke University, Durham, October 19–21. Dr. W. C. Davison, Dean of the Duke University Medical School, was in charge of local arrangements. The program was as follows:

2:45 p.m. Opening.
Dr. Charles Hartwell Cocke, Asheville
3:00 p.m. An Unusual Type of Infection of the Lower Respiratory Tract in College Students.
Dr. W. Reece Berryhill, Chapel Hill
3:45 p.m. The Effect of Renal Injury upon the Regeneration of Plasma Proteins.
Dr. Russell L. Holman, Chapel Hill
4:30 p.m. Round Table Discussion—Diabetes.
Dr. T. Preston White, Charlotte
Dr. W. Raney Stanford, Durham
Dr. Paul F. Whitaker, Kinston
Dr. Roy C. Mitchell, Mt. Airy
6:30 p.m. Informal Supper.
Carolina Inn, Chapel Hill.

President O. H. Perry Pepper of the College was a guest at the meeting and spoke in the evening. Those who could remain were invited not only to attend the program at Duke University on Saturday, October 21, but were also invited to a barbecue lunch and thereafter to attend the Syracuse-Duke football game.

NEW YORK ACADEMY OF MEDICINE—FRIDAY AFTERNOON LECTURES

The New York Academy of Medicine recently announced its fourteenth series of Friday afternoon lectures for 1939–1940, to which the following Fellows of this College will contribute:

Dr. John Russell Twiss, F.A.C.P., Nov. 10, "Medical Management of Disorders of the Biliary Tract";

Dr. Richard A. Kern, F.A.C.P., Philadelphia, Dec. 1, "The Treatment of Visceral Allergies";

Dr. Alvan L. Barach, F.A.C.P., Dec. 15, "Recent Advances in Helium and Oxygen Therapy; Principles and Methods";

Dr. Yale Kneeland, Jr. (Associate), Jan. 5, "Primary Bronchopneumonia";

Dr. J. Burns Amberson, Jr., F.A.C.P., Jan. 26, "Choice of Treatment for Pulmonary Tuberculosis with Special Reference to Newer Surgical Procedures";

Dr. Soma Weiss, F.A.C.P., Boston, March 1, "Types of Syncope and Their Treatment";

Dr. Arthur C. DeGraff, F.A.C.P., March 29, "An Evaluation of Some of the Newer Drugs."

Dr. Francis M. Pottenger, F.A.C.P., Monrovia, Calif., a member of the first Board of Councilors of the American College of Physicians, and serving continuously in some official capacity for the College through 1939, was given a testimonial dinner by the Los Angeles Trudeau Society on the evening of September 26, a day preceding his seventieth birthday. Dr. Pottenger was instrumental in starting anti-tuberculosis work in Southern California with the founding of the Anti-Tuberculosis League, established in 1902, two years before the National Tuberculosis Association was founded. Dr. Pottenger was its first president and served until 1906. The Anti-Tuberculosis League was the ninth organization in the United States for the prevention of tuberculosis; eventually it was merged into the California Tuberculosis Association of which Dr. Pottenger served as president in 1931–32.

In accordance with a long standing custom, former patients of the Pottenger Sanatorium and Clinic, numbering nearly three hundred, gathered on the Sanatorium grounds for the Annual Home-Coming on October 1, further to honor Dr. Pottenger and to recognize his great service to them.

Under the Presidency of Dr. Rodney W. Bliss, F.A.C.P., the Omaha Mid-West Clinical Society held its Seventh Annual Assembly, October 23–27. Scientific exhibits were entered by:

Dr. Albert F. Tyler, F.A.C.P., "Technic of Electrocoagulation";

Drs. E. J. Kirk (Associate) and J. P. Tollman, "A Clinico-Pathological Study of Hypertension";

Drs. F. Lowell Dunn, F.A.C.P. and E. E. Simmons, "Fever Therapy in the Treatment of Rheumatic Fever."

Dr. Clifford J. Barborka, F.A.C.P., Chicago, presented a clinic on "Peptic Ulcer; Gall-Bladder; Obesity," acted as leader of a round table on "The Management of Colitis" and presented two formal papers, "Sub-Clinical States of Nutritional Deficiencies" and "Medical Management of Gall Bladder Disease."

Dr. William R. Houston, F.A.C.P., Austin, Tex., presented a paper on "Learned Reactions." Dr. Samuel A. Levine, F.A.C.P., Boston, gave a clinic on "Organic Heart Disease," led a round table on "Emergency Treatment in Acute Cardio-Vascular Diseases," and delivered two formal papers, "Bedside Diagnosis of Cardiac Arrhythmias" and "Rheumatic Heart Disease."

Dr. J. D. McCarthy, F.A.C.P., acted as Secretary and Director of Clinics. A considerable number of Fellows and Associates of the College from Omaha gave clinics.

Dr. August A. Werner, F.A.C.P., St. Louis, addressed the American Congress on Obstetrics and Gynecology, Cleveland, September 14, 1939, on "The Menopause

and Its Treatment." On September 15, 1939, Dr. Werner was the guest speaker of the Wisconsin State Medical Society at its annual meeting at Milwaukee. The title of his address was "The Sex Hormones." There was also a two-hour round table discussion on this subject.

The Fifth Annual Meeting of the Mississippi Valley Medical Society was held at Burlington, Iowa, September 27–29, 1939. Dr. Sinclair Luton, F.A.C.P., St. Louis, conducted a scientific exhibit on "Digitalis' Major Dosage Error (Difference between Drop and Minims)."

Dr. John W. Shuman, Sr., F.A.C.P., Los Angeles, received the degree of Doctor of Science as conferred by Geneva College last June.

Dr. Marcus W. Newcomb, F.A.C.P., Browns Mills, N. J., superintendent for twenty years of Fairview Sanatorium, Burlington county tuberculosis hospital, was recently honored for his activity in tubercular research by more than four hundred persons at a testimonial dinner.

Dr. Joseph C. Doane, F.A.C.P., Philadelphia, on September 20 delivered the introductory address to the student body of the Woman's Medical College of Philadelphia at the opening of the ninetieth college year of that institution.

Dr. J. Winthrop Peabody, F.A.C.P., Washington, D. C., resigned recently as superintendent and medical director of the Glenn Dale Sanatorium to devote his full time to medical practice. Dr. Peabody was succeeded by Dr. Daniel Leo Finucane, F.A.C.P., who had previously acted as assistant superintendent.

Among guest speakers at the annual meeting of the Indiana State Medical Association, at Fort Wayne, October 10–12, were the following:

Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn., "Some Contributions of the Roentgen-Ray to Advances in Diagnosis";
Dr. Emmet F. Horine, F.A.C.P., Louisville, Ky., "Psychologic Factors in Heart Disease";
Dr. Paul D. White, F.A.C.P., Boston, Mass., "Diagnosis and Treatment of Cardiovascular Emergencies";
Dr. Raphael Isaacs, F.A.C.P., Ann Arbor, Mich., "Diagnosis and Treatment of Pernicious Anemia."

Dr. Nathan B. Van Etten, F.A.C.P., New York City, President-Elect of the American Medical Association, was a speaker at the annual banquet.

Dr. Wardner D. Ayer, F.A.C.P., Clinical Professor of Medicine at Syracuse University College of Medicine, gave a course on organic neurology for the Schoharie County and Montgomery County Medical Societies on six successive Tuesdays, from September 26 to October 31. The course was given under the auspices of the committee on public health and education of the Medical Society of the State of New York.

Dr. Robert Wilson, F.A.C.P., Dean and Professor of Medicine at the Medical College of the State of South Carolina, was the recipient of the 1939 plaque for distinguished service to South Carolina, conferred by the American Legion.

Under the Presidency of Dr. Alexander F. Robertson, Jr., F.A.C.P., Staunton, the Medical Society of Virginia held its seventieth annual session in Richmond, October 3–5. Among speakers on the general sessions program were:

Dr. Franklin M. Hanger, Jr., F.A.C.P., New York City, "Differential Diagnosis of Jaundice";
Dr. Eugene M. Landis, F.A.C.P., Charlottesville;
Dr. Henry B. Mulholland, F.A.C.P., Charlottesville, "The Use of Protamine Insulin in Treatment of Diabetes Mellitus";
Dr. Louis Hamman, F.A.C.P., Baltimore, a clinicopathologic conference.

On October 4, during the state medical meeting, the Virginia Fellows and Associates of the American College of Physicians held their annual regional meeting, details of which will be reported later.

Dr. Wilmar M. Allen, F.A.C.P., superintendent of the Hartford Hospital, Hartford, Conn., has been appointed by the Governor of Connecticut as a member of a commission on the treatment and care of people of the state afflicted with physical or mental disabilities.

Dr. Soma Weiss, F.A.C.P., Hersey professor of the theory and practice of physic, Harvard Medical School, Boston, delivered an address on "Syncope, Collapse and Shock—Mechanism and Treatment" before a joint meeting of the Institute of Medicine of Chicago and the Chicago Society of Internal Medicine, October 27.

The University of Minnesota Medical School, Minneapolis, celebrated its fiftieth anniversary, October 12–14, with a program including clinics, round table discussions, and formal addresses. Dr. Anton J. Carlson, F.A.C.P., Chicago, delivered an address on "The Rôle of the Fundamental Sciences in Medical Progress" and Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, Washington, delivered an address on "Medical Education, Research and the Public Health."

Dr. Bryan M. Riley, F.A.C.P., Omaha, has retired as Dean of Creighton University School of Medicine, being succeeded by Dr. Charles M. Wilhelmj. Dr. Riley had served part time for the past six years as Dean. Dr. Wilhelmj will devote his full time to the work.

Dr. Joseph M. Hayman, Jr., F.A.C.P., has been promoted to Professor of Clinical Medicine and Therapeutics at Western Reserve University School of Medicine.

Under the Presidency of Dr. Charles S. Holbrook, F.A.C.P., New Orleans, the Southern Psychiatric Association held its annual meeting at Louisville, Ky., October 9–10. Among the speakers were:

Dr. John W. Scott, F.A.C.P., Lexington, Ky., "An Internist's Reaction to the Psychoneuroses";
Dr. Oscar O. Miller, F.A.C.P., Louisville, Ky., "Psychiatric Medicine."

Dr. Oscar A. Sander (Associate), Milwaukee, and Dr. Albert E. Russell, F.A.C.P., U. S. Public Health Service, Chicago, delivered papers on "Metal Fume Poisoning" and "Syphilis Control and Its Relation to the Food Industry," respectively,

before the twenty-eighth annual session of the National Safety Congress at Atlantic City, October 16–20.

Fellowships Available in Psychiatry

The National Committee for Mental Hygiene (Dr. George S. Stevenson, 50 W. 50th St., New York City) has announced a limited number of fellowships, provided by the Commonwealth Fund and other sources, for training in extramural, especially child, psychiatry. Fellows will be assigned for one or two years to selected child guidance clinics, the term and plan for each to be determined by his needs. Candidates should have had at least two years of psychiatry in an approved mental hospital, in addition to qualities fitting them for extramural service.

Among the speakers on the program of postgraduate study, sponsored by the Arkansas State Medical Society, at the University of Arkansas School of Medicine, Little Rock, October 10–11, were:

Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn., "Occlusal Disease of the Peripheral Arteries";
Dr. Oliver C. Melson, F.A.C.P., Little Rock, Ark., "The Rôle of the Internist in the Care of Patients with Thyroid Disease";
Dr. Robert L. Schaefer, F.A.C.P., Detroit, Mich., "Clinical Indications of Anterior Pituitary-Like Sex Hormone";
Dr. Paul F. Stookey, F.A.C.P., Kansas City, Mo., "Diagnosis and Treatment of Meningitis."

Dr. William Goldring, F.A.C.P., New York City, addressed the Academy of Medicine of Northern New Jersey at Newark, October 19, his subject being "Clinical Aspects of Hypertension and Arterial Heart Disease."

Dr. George W. Thorn, F.A.C.P., Baltimore, Md., addressed the naval medical and dental officers on duty in the vicinity of the District of Columbia, October 9, on "Supportive Treatment of Infections."

Dr. Walter L. Treadway, F.A.C.P., U. S. Public Health Service, San Francisco, on October 18, delivered a lecture on "The Poor, the Sick, the Bad" at the Mount Zion Auditorium, San Francisco, under the auspices of the Mental Hygiene Society of Northern California.

The Illinois State Medical Society has announced a new program of postgraduate education, to include several one-day conferences and to be held in various cities of the state. The first conference was scheduled for Jacksonville, Ill., November 9, and among the contributors appeared the names of Dr. Robert S. Berghoff, F.A.C.P., Chicago, Heart Disease; Dr. Julius H. Hess, F.A.C.P., Chicago, Pediatrics; Dr. James H. Hutton, F.A.C.P., Chicago, Endocrinology.

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., was named Vice-President of the newly organized Society of Physical Therapy Physicians during its organization meeting in September. The membership in this new society is to be restricted wholly to physicians who devote their practice exclusively to physical therapy. Membership is to be limited to one hundred bona fide specialists who have devoted at least

five years to this specialty and have held or are holding teaching and directoral positions in physical therapy. The president and president-elect are, respectively, Dr. Frank H. Ewerhardt, St. Louis, and Dr. William Bierman, New York City.

Dr. Charles W. Dunn (Associate), Philadelphia, addressed the Medical Society of Delaware at Wilmington, October 9, on "Hormone Therapy: Uses and Abuses."

Dr. LaRue Carter, F.A.C.P., Indianapolis, Associate Professor of Neuropsychiatry at Indiana University School of Medicine, has been named chairman of the division of neurology at that institution.

Dr. Henry N. Tihen, F.A.C.P., Wichita, Kan., has been appointed to the medical advisory committee of the Norton Sanatorium for Tuberculosis.

Dr. Joseph O. Weilbaecher, Jr. (Associate), has been named an assistant director of the Charity Hospital, New Orleans.

Dr. Robert H. Riley, F.A.C.P., Baltimore, and Dr. Ridgely W. Baer, F.A.C.P., president of the Frederick County Medical Society, addressed the semi-annual meeting of the Medical and Chirurgical Faculty of the State of Maryland at Braddock Heights, September 28. Dr. Victor F. Cullen, F.A.C.P., superintendent and medical director of the Maryland Tuberculosis Sanatoria, was acting president of the faculty and delivered the address of welcome.

Dr. William D. Stroud, F.A.C.P., Philadelphia, delivered an address on "Coronary Disease Including Angina Pectoris and Its Differential Diagnosis from Gallbladder Disease; the Indications for Digitalis and Its Administration" before a graduate clinic, August 9, at the Robert Packer Hospital, Sayre, Pa.

Dr. Horace K. Richardson, F.A.C.P., of The Austen Riggs Associates, Stockbridge, Mass., delivered the annual address on "Mental Hygiene in the College Student" at Vassar College on October 2, 1939.

Dr. Harold G. F. Edwards, F.A.C.P., Shreveport, addressed the members of the Third International Cancer Congress at Atlantic City, Sept. 11 to 15, his subject being "Carcinoma of the Cervix; A Study of 656 Cases."

OBITUARIES

DR. EMIL GEORGE VRTIAK

Dr. Emil George Vrtiak (Associate), Chicago, Ill., died August 7, 1939, of coronary occlusion.

Dr. Vrtiak was born in Czechoslovakia, March 17, 1890. He received the bachelor degree from the University of Illinois in 1917, and the medical degree from Rush Medical College in 1920.

For many years Dr. Vrtiak had been interested in arthritis and in addition to studies made in the Clinic he returned for European study in 1924

and 1929. Dr. Vrtiak was an excellent teacher and at the time of his death was Associate Professor of Clinical Medicine at Rush Medical College.

He was a member of the staff of the Lutheran Deaconess Hospital and the Norwegian-American Hospital. He was a member of a number of medical societies including the American Medical Association, the American Association for the Study and Control of Rheumatism, the Bohemian Medical Society of Chicago, of which he was past president, and the Institute of Medicine of Chicago, and had been an Associate of the American College of Physicians since 1936.

Dr. Vrtiak was a hard worker, a thorough student, and an excellent doctor. In addition to care of patients, he did much for the welfare of the Czechs in Chicago. His patients recognized not only his medical interest in their difficulties but his extremely human attitude and his concern for their welfare.

ERNEST E. IRONS, M.D., F.A.C.P.

DR. JOHN A. MACGREGOR

The death of Dr. Macgregor occurred suddenly at his home in London, Ontario, on September 20, 1939, and with his passing the University of Western Ontario has suffered a serious loss, for Dr. Macgregor had been a strong stabilizing influence in the medical school and wielded a powerful influence over the student body.

Dr. Macgregor was born in Lanark County, Ontario, and graduated from University of Western Ontario Medical School in the Class of 1892 at the age of nineteen years.

Following his graduation he was a demonstrator at the medical school for one year, and then he established a general practise at Kent Bridge, near Chatham. He later practised for a time at Minden, Nebraska, and finally returned to London, Ontario, in 1905.

Following his return to London he became professor of pathology and bacteriology at the Medical School and in 1920 he was promoted to the post of Professor of Medicine. In 1925 he was made professor emeritus.

His contributions in the field of medicine were many and as a member of various medical associations he became well known in the profession.

Dr. Macgregor was a Fellow of the American College of Physicians, and a member of the American Medical Association and the Canadian Medical Association, and was a past president of the Ontario Medical Association. He was also a Fellow of the Royal College of Physicians (Canada).

In 1931 his valued contributions to the University of Western Ontario were formally recognized when he received the degree of LL.D.

Dr. Macgregor is survived by his wife, Mrs. Matilda (Langford) Macgregor, and one son, Dr. L. S. Macgregor of Kitchener, Ontario.

J. H. HOLBROOK, M.D., F.A.C.P.,
Governor for Ontario.

DR. HAROLD LEVI RYPINS

Dr. Harold Levi Rypins, F.A.C.P., of Albany, N. Y., died on August 25, 1939, at the age of forty-five years.

Dr. Rypins was born on December 21, 1891 at Evansville, Indiana. He received his A.B. degree from the University of Minnesota in 1914; attended Columbia University School of Journalism and then received his M.D. degree from Harvard University Medical School in 1919. He was Assistant Professor of Medicine at the Albany Medical College and was formerly an Associate and Instructor in Medicine there. He was Instructor in Medicine at the University of Minnesota Medical School in Minneapolis from 1920 to 1923; Secretary of the New York State Board of Medical Examiners; past President of the Federation of State Medical Boards of the United States; Member of the National Board of Medical Examiners; Member of the Executive Committee of the Advisory Council on Medical Education; Executive Secretary of the Medical Grievance Committee of the State Education Department; Fellow of the American Medical Association and Fellow of the American College of Physicians since 1934.

Dr. Rypins is survived by his widow, three children and a host of friends throughout the country.

CHARLES F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York.

DR. GEORGE HOLT BARKSDALE

Dr. George Holt Barksdale, F.A.C.P., Charleston, W. Va., was born in Alderson, Monroe County, West Virginia, August 15, 1882; died October 8, 1939, of a heart attack at his home in Charleston.

Dr. Barksdale received his M.D. degree from Northwestern University Medical School in 1908. He served his interneship in St. Luke's Hospital, Chicago, and received postgraduate training at St. Luke's Hospital, Chicago, Massachusetts General Hospital, Walter Reed Hospital, Washington, D. C., New York Neurological Institute, and in Vienna. He was formerly Assistant to Owner, Fabiola Hospital, Eveleth, Minn., and Director, Hill Crest Sanitarium, Charleston. He was a member of the Staff of St. Francis and Charleston General Hospitals; author of several publications; and during the World War served as Chief of Medical Service and Chief of the Tuberculosis Board at U. S. Army General Hospital 42, Spartanburg, S. C., with grade of Major, Medical Corps.

Dr. Barksdale was a member of the Kanawha County Medical Society, West Virginia State Medical Association and the American Medical Association. He was ex-President and ex-Vice President of the West Virginia Heart Association; ex-President of the Charleston Journal Club; ex-President and Member of the West Virginia Tuberculosis and Health Associa-

tion; and had been a Fellow of the American College of Physicians since 1936.

Dr. Barksdale is survived by his wife, two sons and one daughter.

ALBERT H. HOGE, M.D., F.A.C.P.,
Governor for West Virginia.

DR. THADDEUS WALKER

Dr. Thaddeus Walker, of Detroit, Michigan, an Associate of the American College of Physicians since 1926, died June 13, 1939. He was born in Walkerville, Ontario, in 1869. Following graduation from the Detroit College of Medicine in 1893, he spent three years in graduate work in Berlin, Vienna, and Edinburgh. On his return, he started practice in Detroit, and as his interest lay largely in pathology and clinical laboratory procedures, he founded the Detroit Clinical Laboratory, the first of its kind in the city.

Dr. Walker served during the Spanish American War as a Contract Surgeon. He retired from active practice in 1912. He was an Honor Member of the Wayne County Medical Society, which he had ably served in its earlier days of growth and expansion. He also held membership in the Detroit Academy of Medicine.

Dr. Walker's passing will be mourned by a host of friends, as well as by his professional colleagues of the city.

HENRY R. CARSTENS, M.D., F.A.C.P.,
Governor for Michigan.

DR. BAYARD G. KEENEY

Dr. Bayard G. Keeney, F.A.C.P., Shelbyville, Ind., died suddenly on October 11 while attending the annual convention of the Indiana State Medical Association in Fort Wayne, aged 63 years.

Dr. Keeney was to have served as Chairman of the Section on Medicine of the State Association at the Wednesday afternoon Session, and his son, Dr. Edmund L. Keeney, of Baltimore, was to have been one of the guest speakers on the Thursday morning program.

He received his M.D. degree from the University of Cincinnati College of Medicine in 1902, and then did postgraduate work in Europe.

Dr. Keeney was Shelby County Health Commissioner for six years, and always was active in civic and medical society work. He was a member of the Shelby County Medical Society, Indiana State Medical Association and the American Medical Association, and had been a Fellow of the American College of Physicians since 1930.

ROBERT M. MOORE, M.D., F.A.C.P.,
Governor for Indiana.